THESIS.

A Study in the Treatment of Essential Hypertension

Comprising

An Account of the Results in 64 Patients Treated By Combined Oral Pentolinium Tartrate and Rauwolfia Serpentina

Compared with

The Results in a 2 - 10 Year Follow-up in 64 Patients following Lumbo-Dorsal Sympathectomy.

by

D. S. Harling.

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This paper is concerned with the study of two series of patients suffering from essential hypertension.

The significance of the term has recently been examined and a new concept advanced.

The Concept of Essential Hypertension.

Historical.

Richard Bright (1827) made the first significant correlation of albuminuria, dropsy and renal disease and demonstrated also nine years later, the occurrence of cardiac hypertrophy in renal disease. He appeared to realise, before the invention of the sphygmomanometer, the existence of arterial hypertension as the connecting link between renal disease and cardiac hypertrophy. The connection between them was first definitely established by Traube.

In the years after Bright, elucidation of the individual diseases grouped under his name continued, but there came the realisation that the symptom of hypertension was not invariably a consequence of pre-existing renal disease or of arteriosclerosis.

Mahomed (1874) described the pre-albuminuric stage of Bright's disease.

Von Basch (1893) described cases in which there was a high tension of the pulse, but in which

other characteristics of outspoken arteriosclerosis were absent or minimal - a state which he named latent arteriosclerosis. Allbutt (1895) recognised isolated hypertension with little renal involvement, calling it hyperpiesia. He distinguished it from Bright's disease, with or without high blood pressure, and from decrescent arteriosclerosis, which is the senile atheroma of large arteries, and which is not necessarily associated with high blood pressure.

Huchard at this time recognised the frequency of non-nephritic hypertension and called it pre-sclerosis. This he did in order to emphasise his belief that the hypertension antedated the sclerosis. Frank (1911) called the condition essentielle hypertonie, a term which is translated as essential hypertension. In Volhard and Fahr's classification of Bright's disease, the condition is included in section C - as benign hypertension under the heading scleroses, the other headings being the nephroses and nephritides.

Present Concept of Essential Hypertension.

The current concept of essential hypertension would thus include those patients with high blood pressure in whom none of the known causes of clinical hypertension is demonstrably operative. It seems almost certain that the designation of

essential hypertension is merely a collective concept for a number of conditions in which arterial hypertension is evident, but in which there is no known reason for its presence. This is the opinion held by Fishberg (1955).

Pickering: New Concept of Essential Hypertension.

The foremost of the recent work on high blood pressure is the contribution to the subject by Professor Sir George Pickering - High Blood Pressure - Churchill, (1956).

The data assembled by Pickering led him to conclude that essential hypertension is polyphiletic in origin: that age, inheritance, environment and sex are the only known factors in its etiology, and that these factors affect, in varying ways and degrees, the whole population and that there is no sharp division between normal blood pressure and hypertension.

Pickering, in approaching the problem of defining normal, and pathologically high blood pressure, but specifically excluding secondary hypertension, outlines three possibilities.

1. Normal and high pressures may differ qualitatively, so that there is a sharp division between them.

2. Normal and high pressures are qualitatively different, but overlap to a considerable extent.

3. There is no qualitative difference between normal and high pressures.

He records his investigations and concludes that normal blood pressure and hypertension are not clearly defined and separate. He concedes that consistent with the facts are two possibilities - the first, that normal blood pressure and hypertension may be qualitatively different and may overlap, and the second, that they may be quantitatively different. But from the genetic analysis he believes that arterial pressure is a graded characteristic and that in effect, the difference is quantitative.

His concept affirms - that essential hypertension is not a disease entity. It is the name given to a collection of subjects with high blood pressure, in whom no specific lesion has been found to account for the high pressure. Essential hypertension in fact represents the right hand end of frequency distribution curves which show continuous variation. There is no such thing as a dividing line between normality and hypertension, but merely degrees of hypertension. The differences are in fact quantitative.

Pickering, in the light of this concept, discusses the continued use of the term essential hypertension and he believes that it may still be

of value. He considers however, that the term should be reserved for those individuals with the higher ranges of blood pressure, in whom there is increased liability to vascular disease, with consequent decreased expectation of life and in whom, in the higher ranges, there is the possibility that the malignant phase will develop. The series of patients, whose records are presented in this paper, are, in the great majority of cases, embraced by the above definition of essential hypertension, for in only three instances are the initial diastolic blood pressure readings, less than one hundred and twenty millimetres of mercury.

Hypotensive Therapy in Essential Hypertension.

The assessment of the value of various therapies advocated, throughout the years, presents various difficulties.

1. The decision of the levels of blood pressure which constitute hypertension has been an arbitary one and the levels accepted have varied in different series.
2. The definition of essential hypertension has not, up till now, involved a purely quantitative concept. Selection has, therefore, frequently been prominent so that case material in different series is not strictly comparable on clinical grounds.

3. There appear to be only two valid methods of gauging success in treatment, the first, the increase effected in life expectation, and the second, the improvement made in the patient's immediate condition. The former requires controlled series which are not always available, while the latter depends in large degree on subjective experiences of the patient. This is not always easy to assess.

For these reasons, the literature is full of conflicting claims in favour of the particular agent most widely used at that particular time.

Nitrites and Nitrates.

Though at one time they enjoyed great popularity, these drugs, after careful trial and consideration did not prove to be of value in significantly lowering the blood pressure. They need not be considered further.

Thiocyanates.

The use of thiocyanates in recent medicine is due to Barker (1936) who devised a scheme of treatment control by estimation of the serum thiocyanate level. Prior to this, their earlier rejection was almost certainly associated with the many side effects resulting from uncontrolled dosage. The side effects, some mild, others

severe, bear a quantitative relation to the dose employed.

The mechanism of the hypotensive action is unknown.

Clinical reports on their efficacy in hypertension vary widely. Goldring and Chasis, (1932) reported 31% of significant blood pressure reduction with concomitant symptomatic improvement. As however, there were some patients who showed symptomatic improvement without reduction in blood pressure, they considered the improvement which occurred, was largely psychic.

The occurrence of symptomatic improvement where no reduction of blood pressure is evident, is common to many other agents employed in the treatment of hypertension, viz. lumbo-dorsal sympathectomy, and methonium compounds. This unexplained and unexpected dividend in therapies designed to reduce the blood pressure, has always been a contentious point in assessing their true value.

Goldring and Chasis however, found because of their toxic effects, no justification for the use of thiocyanates in hypertension.

Later studies on the other hand suggest that thiocyanate therapy controlled by blood levels of serum thiocyanate, achieved considerable reduction in blood pressure in a proportion of selected

patients and symptomatic relief in a greater number. The extent of benefit, which was claimed, however, varied. Barker (1941) reported relief of symptoms and reduction of blood pressure in 47% of patients Palmer (1942) comparing thiocyanate therapy with sympathectomy, reported adequate blood pressure reduction in only 20% of patients.

Sympathectomy.

Rowntree and Adson performed the first lumbar sympathectomy for hypertension in 1925. Adson and Allen, and also Smithwick (1940) published reports of their own operated cases.

The rationale of the operation is the lowering of the blood pressure by a decrease in peripheral resistance, due to dilatation of small blood vessels severed from their sympathetic innervation. Dilatation of the splanchnic vessels and pooling of blood in the dependent parts of the body, play major parts in the blood pressure reduction.

The techniques employed vary. From the original lumbar and splanchnic sympathectomy of Adson, Smithwick developed his thoraco-lumbar sympathectomy, D9 - L2 extended later to D4, and Grimson performed the subtotal sympathectomy, including stellate ganglionectomy.

The most widely adopted procedure is the Smithwick operation. The extension of section

was an attempt to diminish the proportion of failures which resulted from the more limited section.

Pickering records the results in combined series of 142 patients - 18% were satisfactorily controlled at 2 years. He conceded that the operations do provide a small number of outstanding successes, but he underlines the objection that they cannot be predicted. He is not completely satisfied that the claims by Hammerström and Bechgaard, and by Smithwick also, for increased life expectation are conclusively proved. Most reports agree that permanent reduction in blood pressure is achieved only in a comparatively small percentage of cases. They stress however, that considerable discomfort lasting many months, may follow the operations, particularly pain and postural dizziness. The symptomatic relief to the patient in even unsuccessfully controlled cases is not always emphasised or even accepted, though Fishberg, in a series of 119 patients, found improvements in symptoms, electrocardiographs, heart size and retinal changes over and above the proportion of reduced blood pressures.

Disappointment with the uncertain results of surgery prepared the field for the next widely employed therapy in hypertension.

The Methonium Compounds.

These drugs were developed concurrently by Barlow and Ing (1948) and Paton and Zaimis (1949). They are quaternary ammonium compounds. They produce by a selective action on the postsynaptic membrane, ganglionic blockade which results from the elevation of the threshold of the ganglion cell to acetyl choline liberated by the pre-ganglionic nerve volley.

Hexamethonium is a bis-quaternary ammonium, with six carbon atoms on the inter nitrogen chain. Pentolinium tartrate (pyrrolidinium bitartrate, ansolysen) has the quaternary nitrogen in a hetero cyclic ring. It is more potent and is longer acting than hexamethonium.

Hexamethonium (C6) is considered as homologue for the group. C6 has a selective action on various autonomic ganglia, and it is possible that agents with a high degree of selectivity for a particular set of autonomic ganglia, will be developed.

Autonomic blockade produces a lowering of blood pressure and peripheral blood flow is enhanced. The cardiovascular responses to peripherally acting hypertensive and hypotensive drugs are exaggerated in individuals under the influence of hexamethonium blockade, probably because of ganglionic interruption of normally

operating compensatory autonomic reflexes. The drugs induce a hypotensive response even in sympathectomised patients, probably because there are ganglionic vaso-constrictor pathways which are not removed by surgery.

Sodium depletion, sympathectomy and hypertensive encephalopathy increase the hypotensive effect of C_6.

It is of particular importance to consider the effects of the hexamethonium group of drugs on renal function. A single intravenous injection of a hypotensive dose of C_6 has either no effect on renal vascular resistance or it causes an increase in renal vascular resistance (RVR) - so that glomerular filtration rate (GFR) and renal plasma flow (RFF) are reduced at the time of maximal reduction in blood pressure. However, despite continued hypotension, recovery occurs in about an hour.

In malignant hypertension the chronic hypotensive action of C_6 may cause progressive renal insufficiency and uraemia with a rapidly fatal outcome. The effect of pentapyrrolidinium on renal function is similar to that of hexamethonium, V-Rønnov-Jessen (1955). C_6 is active in blocking visceral parasympathetic ganglia. This action is responsible for some of the undesirable side effects of hexamethonium therapy.

Intractable constipation is sometimes troublesome and ileus has been frequently reported. Difficulty in micturition is occasionally experienced. Decreased salivation with annoying dryness of the mouth is also an effect of parasympathetic blockade.

The methonium group of drugs has however almost completely replaced others in the treatment of hypertension. Hexamethonium was the first member of the group to be extensively used, and parenteral injections were favoured for certainty of effect. Pentapyrrolidinium is five times more potent than hexamethonium and is more regularly absorbed from the intestine than hexamethonium. Oral therapy is now a practical procedure.

The value of methonium therapy is established by an increase in the life expectancy achieved in malignant hypertension. Indeed, Smirk (1954) reports that after six years, 57% of his group IV cases are still alive, when the expected survival is 2%. These results are achieved by parenteral therapy. The value of oral therapy is not so readily established, particularly in grades of hypertension where the actual outcome without treatment, is disputed and the present paper presents my own experience and conclusions.

Veratrum Alkaloids.

Baker first employed these drugs in the

treatment of eclampsia in 1859. Obtained from liliaceous plants, they have been used for medicinal purposes since the Middle Ages. Veratrum viride contains about twenty alkaloids. The precise pharmacological actions of this group are not definitely established. A reflex fall in blood pressure is achieved, mediated by probable reflex inhibition of central vaso-constrictor impulses and a peripheral vaso-dilatation results. There is no ganglionic blockade. Cerebral circulatory resistance is significantly decreased.

The main function of the veratrum alkaloids appears to be in the treatment of eclampsia when continuous intravenous injection produces a fall in blood pressure and a slowing of the heart rate. When employed orally the therapeutic dose of veratrum viride is close to the toxic dose.

Hydralazine.

L-hydrazinophthalazine hydrochloride - apresoline, lowers the blood pressure and augments renal blood flow. It increases cardiac rate and output, which effects result,apparently,from central sympathetic stimulation.

The hypotensive effect is due to a vaso-dilatation, predominantly splanchnic - and the site of action may be central either on the vaso-motor centres or on the hypothalamus.

Hydralazine may be used intravenously in hypertensive encephalopathy, but its main use is by mouth. There are several unpleasant side effects - headache, vertigo, nausea, joint pains, drug rash; and Dustan reports a syndrome resembling lupus erythematosus following its use. Blood pressure levels are lowered, but not to the same extent as with the methonium compounds. Its value may be greatest, in combined therapy, owing to its effect in enhancing renal blood flow. This has been emphasised by Harris and Turner (1954).

Rauwolfia Serpentina.

Roots of this plant have been used in India for centuries. Bhatia (1932) brought it to wider notice for use in hypertension.

There are at least five generically different preparations of Rauwolfia.

1. Ground rauwolfia root containing reserpine-like alkaloids.
2. Alseroxylon fraction containing reserpine and rescinnamine.
3. Reserpine, a single alkaloid.
4. Rescinnamine - distinctly less sedative than reserpine.
5. Cannescine. Maison (1955).

Rauwolfia Serpentina has a mild hypotensive action, and it tends to stimulate the bowel. There is too, a tendency to produce depression,

especially in patients who have previously shown mental instability. Smirk and McQueen (1954) reported a 10% incidence of mental disturbance in a series of patients treated with reserpine. Studies of the various preparations, whole root, reserpine, rescinnamine, and more recently, canescine, do not reveal any convincing difference of one over the other, in respect of this tendency to produce depression.

At present its main use in hypertension appears to be in combination with other drugs, particularly with pentapyrrolidinium, where there are good grounds for regarding their hypotensive effects as synergistic.

Rauwolfia has been used most often in combination, but it is becoming recognised that this drug has a value in use alone, as Platt (1956) reports. The preparation used in this study has always been the "Serpasil" brand of reserpine.

Mecamylamine.

This is also a ganglion-blocking drug, but is not a quaternary ammonium compound. A secondary amine, it is absorbed in a regular fashion from the alimentary tract.

It is at present achieving success in the treatment of hypertension and may come to occupy the position of hexamethonium and

pentapyrrolidinium, but its place is not yet established.

Its action is not quite similar to the methonium compounds in its ganglion blockade, and further, it has a direct effect on the intestine and the heart, as has been demonstrated by Bennett, Tyler, Zaimis (1957).

The Classification of Patients with Essential Hypertension.

Various systems have been advanced for the grouping of hypertensive patients. This grouping is required to allow comparison with published series in respect of prognosis and to establish the grade of severity of the patients under study.

The choice of classification has been carefully considered. The systems studied were -

(i) Keith, Wagener and Barker, 1939.

(ii) Rogers and Palmer, 1946.

(iii) Hammarstrom and Bechgaard, 1950.

(iv) Smithwick, 1951.

(i) Keith, Wagener and Barker.

Keith and Wagener outlined their criteria for classification in the American Journal of Medical Science in 1939 and in this account and in their other publications in 1933 and 1939 give guidance in its application.

From the retinal findings which form the bases of their classification 4 groups are recognised.

Group I - Mild narrowing or sclerosis of the retinal arterioles.

Group II - Moderate to marked sclerosis of the retinal arterioles.

Group III - Angiospastic retinitis.

Group IV - The findings in group III, with in addition, measurable oedema of the discs.

Thrombosis of the retinal veins, or retinitis of the arteriosclerotic type may occur in Group II. Further details of the ophthalmoscopic criteria for their classification are given in their papers. The 219 cases they classified in this way are seen to fall into well recognised groups, the clinical patterns of which are described and the prognosis in the individual groups are recorded.

As directed by Keith (1939) the height of the blood pressure, the effect of rest on the levels recorded over 24 hours, the symptoms complained of and the progress over several months, have, in company with the retinal findings, to be taken into consideration in deciding whether some patients belong to Group I or Group II. Further, good cerebral, cardiac and renal function is a necessity for Groups I and II.

(ii) Rogers and Palmer.

A system of classification was proposed by Rogers and Palmer, 1946, and the outcome after four, eight and twelve years of non-specific medical therapy in 646 patients so graded, is described in this paper and in two further accounts - Palmer, Loofbourow and Doering, (1948) and Palmer and Muench, (1953).

This system is developed from and adopts Keith's retinal grading. In addition, the clinical state and function of heart, brain and

kidneys is assessed and allotted grades - normal (0), slight (1), moderate (2) and severe (3) as follows:-

The Heart.	Grade 1.	Slight enlargement (radiological or clinical).
	2.	Greater enlargement than in 1, but no failure (anginal or congestive).
	3.	Actual or impending anginal or congestive failure.
The Kidney.	Grade 1.	Slight albuminuria, with or without casts, but no impaired function.
	2.	Slight albuminuria and minimal numbers of formed elements or slightly impaired function.
	3.	Marked impairment of renal function with marked abnormality in sediments.
The Brain.	Grade 3.	Achieved by any patient who has had a cerebral thrombosis or haemorrhage.

The highest grade achieved in any area is the final grade for the patient - 0, 1, 2 or 3 and papilloedema, even with no other abnormality will always achieve grade 4.

This system is definite in its criteria and simple to apply and control. Surgically treated series are published in the references above and by Palmer (1947).

Their classification was not adopted for the present series for these reasons:

1. It implies prognosis, based on the arteriosclerotic complications of hypertension but the ability to assess prognosis accurately when based on these complications is not universally accepted.

For example, a patient who has had a cerebral thrombosis is placed in grade 3, though the heart, kidneys and fundi are normal. It must be conceded that the presence of a significant degree of arterio-sclerosis which such an incident reveals, will affect the prognosis of a hypertensive patient unfavourably, and Rogers and Palmer, and also Smithwick, employ the occurrence of these incidents, to assess prognosis and allot such events a numerical value. This does not seem to me to be justified; and to support my contention I have quoted in the conclusion to this section Keith's views on the subject published in 1939. The views he advanced then do not yet appear to require amendment.

2. Though based on Keith's retinal grading and by inference accepting his prognostic conclusions, it appears to contradict them. In the example cited in the last paragraph, the patient would fall in the same grade as one showing angiospastic retinopathy - a pre-malignant state, yet the outcome may be markedly dissimilar in the two cases.

Further, a severe grade of narrowing reflecting the severity of hypertension may rate grade 2 in Keith's concept, yet only grade 1 in this system, while irregularity indicating retinal arterio-sclerosis, scores grade 2.

3. The levels of blood pressure in the cases described where diastolic pressures of 110 mms. of mercury and below are reported to occur not rarely in grades 1 and 2. and not in excess of 110 mms. in a few cases in grade 3, are of an order not appearing in the pre-treatment records of the two series to be described.

4. A study of the composition of group 3, if patients with hypertension are classified according to the criteria of Rogers and Palmer, is made possible by the following percentage composition of the group, published in their paper in 1947. The group is labelled the late stage of benign essential hypertension - Grade III and comprises:-

19% advance mild grade to late grade 3 hypertension;

17% incidental hypertension in old age;

24% mostly hypertension discovered accidentally in middle life with cerebro-vascular accidents, coronary heart disease or chronic vascular complications;

10% precocious sclerosis in young adults;

23% unclassified.

A study of this list will immediately establish that these figures have little bearing on the series of patients whose records I have presented, for in the latter, hypertension is considered to be contributory in a major degree.

I believe that Rogers' and Palmer's

classification is of value in grouping and in comparing unselected series of cases with high blood pressure, but it is of less value in grouping selected patients, referred for treatment of essential hypertension.

(iii) Hammarstrom and Bechgaard.

Hammarstrom and Bechgaard (1950) followed a series of 251 operated cases for 1 - 8 years. Because the patients in Bechgaard's 1946 series of 1,000 non-operated hypertensives had not been selected, they were unable to accept the latter as suitable for comparison with a necessarily selected surgical series. Therefore, as a control, a non-operated series, was assembled by selection, from the records of 130,000 patients in Danish hospitals and this control series was followed up for 2 - 10 years.

The selection they employed was on the basis of the same criteria they had devised for the selection of their cases in the surgical series and 435 non-operated cases were followed up and available for the control series.

The criteria for selection were:-

Group 1. Uncomplicated hypertensive disease without subjective symptoms.

Group 2. Marked subjective symptoms, but without myocardial damage - the patients may show left axis deviation in the E.C.G. and/or relative enlargement of the left ventricle, if the heart volume is within normal limits according to teleradiography. Retinal findings 1 or 2 Keith.

Group 3. Patients who in addition show one or more of the following signs of cardiovascular damage. Negative T_1 in the electrocardiograph, heart volume above the predicted normal/500 ml/M^2 body surface in men and 450 ml/M^2 in women, or the transverse diameter of the heart greater than one half the inner thoracic diameter; residual damage after cerebral insult; and constant albuminuria.

Group 4. All hypertensives with definite retinal exudates and/or papillary protrusion.

All the data required for this classification were not available so it could not be employed here. A comment on its implications is not however out of place:-

Attention is paid to symptoms and the grouping provides a clinical estimate of progress of the hypertensive state. However there appear to be three serious objections.

1. The electrocardiographic changes specified (negative T_1 in the electrocardiograph) may occur in patients in whom hypertension is absent, and such electrocardiographic changes may not be present, when the hypertension is severe.

2. The combination of Keith's grades 3 and 4

into one group IV implies non-acceptance of Keith's work in separating them. This does however, have the considerable disadvantage of distinguishing the patients with angio-spastic retinopathy from those who demonstrate vascular complications of hypertension without these retinal changes.

3. Again, however, the vascular complications are favoured with prognostic implication.

(iv) Smithwick.

Smithwick's classification (1951) proposed the following criteria designed to facilitate close comparison of medical and surgical series. It involves a points system with the awarding of a numerical value to various factors which have a bearing on prognosis, as follows:-

	Numerical value of each factor.
+ Cerebro-vascular accident with or without minor residual. Abnormal electrocardiogram. Enlarged heart. Impending failure. P.S.P. less than 25% in 15 mins. or less than 60% in 2 hrs. Age 50 or over. Mild angina.	1
Cerebro-vascular accident with residual. Frank congestive failure, moderate angina P.S.P. less than 20% in 20 mins. Unsatisfactory response to sedation.	2

+ i.e. cerebral deterioration or definite involvement of arm and/or leg.

	Numerical value of each factor.
P.S.P. less than 15% in 15 mins.)	3
Nitrogen retention.)	4

(a) If the numerical grade is less than 4, the patient will be in either group 1 or group 2. Changes in cerebral, cardiac or renal areas, or the presence of Keith's retinal grades 2, 3 or 4 will ensure the patient is in group 2.

(b) If the numerical grade is 4 or more, the patient will be in group 3 or 4. A resting diastolic pressure over 140 mms., or cerebro-vascular accident with marked residual, combined with a poor response to sedation, will place the patient in group 4.

This system demands details which were not always available in our patients and it therefore could not be applied. The following observations however, seem pertinent.

In group 2, there may appear patients with retinal grades 2, 3 or 4 in accordance with Keith's classification. This is an apparent denial of Keith's conclusions: Yet Smithwick so graded according to Keith, 192 patients referred to him and treated non-surgically, the outcome so closely parallelling Keith's results, that he was content to combine both series to use as a non-surgical control. Again, patients with equivalent

electrocardiographic changes and heart enlargement would score group 4, if they exhibited residual damage following a cerebro-vascular accident and would score only group 3 without residual damage after a cerebro-vascular accident, implying prognostic significance in the degree of arterio-sclerotic manifestations of hypertension.

Smithwick's reliance on sedation tests as a valuable screening method has not been confirmed in preliminary studies for this series, and his suggestion that surgery might seriously be considered in young adults with diastolic blood pressures of 110 mms. of mercury or more envisages a wider indication for surgery than that employed in the selection of the surgical series in this study. Examination of the pre-operative blood pressure records of the surgical series on page 38 will establish the latter point.

It must be that Smithwick with his unrivalled experience of surgery for hypertension, has evolved a system which he personally has found to be accurate in assessing the outcome of surgery in the vast numbers of patients referred to him.

For the present smaller series, however, his system demands data, not available in all the patients and Keith's grading is still preferred, after a close study of the foregoing method.

A proposed grouping for patients suffering from hypertension, by Leishman (1953), is of value in underlining prognostic factors.

151 patients were followed for five years and certain general conclusions which were arrived at, are stated below.

(a) The accuracy of Keith's retinal gradings are confirmed.

(b) The stage which the hypertensive disease has reached, regardless of the height of the blood pressure, is best judged from the presence or absence of 4 clinical features.

Advanced retinal change.
Albuminuria in excess of a trace.
Cardiac enlargement.
Abnormality of the E.C.G.

(c) As Leishman stated in his report, "Hypertensive disease must be regarded as inevitably progressive, but the speed of development is infinitely varied in different patients and two groups are generally recognisable". These two groups he is able to distinguish, are termed benign hypertension and the other accelerated hypertension.

1. Benign Hypertension. This occurs mostly in women and diastolic pressures are consistently nearer 100 than 120 mms. Retinal change is never more than grade 2; rarely is there more than a trace of albumin, and rarely more than a loss of

urine concentrating power. Further, the electrocardiogram is only abnormal when the heart is considerably enlarged.

2. Accelerated Hypertension. A sudden change from benign hypertension to the accelerated process is rare (only 2 in 200 of his patients exhibited this change). The heart enlarges progressively and these patients usually die of congestive heart failure.

Conclusion.

The various systems have been studied and the grouping of Keith is preferred for the reasons given. There is however one important proviso.

The 219 patients in Keith's series, from which he outlined the prognostic implications of retinal grading, belonged to a selected group.

Keith in his publication of 1939 affirmed:- "In the present attempt to group cases of essential hypertension clinically, we realise that not all, fall into one of the four groups mentioned. There are many patients who have, in addition to arteriolar dysfunction, diffuse arteriosclerosis more especially of the aorta and coronary and cerebral arteries. Atherosclerosis of the arteries may be the determining factor as to the course and prognosis. With more knowledge relative to the occurrence of atherosclerosis in

in such vital internal arteries and with the aid of more accurate diagnostic methods, these cases might be grouped in a much more satisfactory manner than is possible at present".

In both series to be described in this paper patients in this category, i.e. retinal grade 1 or 2, but with coronary disease, cerebro-vascular accident or congestive failure, all betokening serious functional derangement, exhibit complications which prevent their inclusion in the corresponding Keith groups and they are listed ungrouped. This point was clarified in a personal communication (Keith).

The Investigation - Introduction.

The following is an account of the results of treatment of two series of patients suffering from essential hypertension, admitted to Derbyshire Royal Infirmary and Derby City Hospital.

The first series of 64 patients comprises all cases subjected to bilateral lumbo-dorsal sympathectomy for the above complaint, the operations being completed between 1946 and 1954.

The second series of 64 patients comprises, with one exception, all cases initiated in therapy with oral pentolinium tartrate (ansolysen) and rauwolfia serpentina (serpasil) in the medical wards of the two hospitals, during 1954 and 1955. (The exception is a lady who refused to attend a special follow-up clinic though she is in fair health).

The exact approximation of the number in each series is accidental, but fortunate.

All patients in both series were admitted to the medical wards, following out-patient observation, in many instances, of considerable duration. In a number of patients in the surgical series, potassium thiocyanate had been used prior to operation. In the medical series previous therapies included, in some patients, potassium thiocyanate, oral or subcutaneous hexamethonium

bromide and, in a few, prior lumbo-dorsal sympathectomy.

Medical supervision has been common to both groups since the same group of physicians who selected, investigated and referred for surgery the first series have been responsible for the medical supervision of the second series. In addition, radiological examinations were made by one radiologist and ophthalmoscopic examinations were carried out, in the great majority, by one ophthalmologist.

I have personally conducted follow-up clinics of both series during the last four years.

Selection has operated in the choice of cases comprising both series, but this selection has been entirely outside my control. The selection has been solely the selection of the therapy considered by the physician-in-charge, to be appropriate to the individual patient at the time. During the periods under survey, many patients treated by drugs other than the combination under study, attended the same follow-up clinics. In two cases covered by the period of medical series parenteral administration of ansolysen was considered imperative in view of the urgency of the clinical state. Those in which treatment was administered by drugs other than the combination under study, or

by ansolysen, parenterally administered, are not the concern of this paper.

A possible bias in favour of the surgical series may operate, for there were some severely ill hypertensives who were considered to be beyond the help of surgery - but as will be seen from the clinical details of the surgical series, surgery was undertaken in some seriously ill patients.

The surgical series has been followed up for five to ten years and the medical series for six months to two years.

Objects of the Survey.

The surgical series is presented -

1. To record the results of treatment after six months and in follow-up examinations extending to ten years after operation.
2. By means of grading patients to draw comparisons in prognosis:
   (a) with published figures for the natural outcome (without specific therapies) in these grades;
   (b) with published figures for other series of surgically treated patients.
3. To provide a standard series, graded, followed up for over five years and established by comparison with published figures, against which to measure the effects of treatment in the medical series.

The medical series is presented -

1. To record the results of treatment, at the end of six months and to date, in some cases two years after initiation of treatment.

2. To compare the initial results of medical treatment on prognosis, symptoms and objective findings with the results in the standardised surgical series (see para. 3 above). It has to be emphasised that patients in the medical and surgical series were graded in the appropriate classifications by the same observer using the same criteria for his grouping in either series. Further all patients in both series were examined and selected by the same physicians, with the same experts to assist them.

(It is felt that, in this way, some of the disadvantages inherent in comparing results of medical and surgical treatment from different centres, will disappear).

Investigation of Cases.

Blood pressure readings. The initial blood pressure reading taken at the first formal examination after admission, with the patient reclining in bed, is the base-line level adopted, against which to measure the effects of treatment. The initial blood pressure reading has been in most cases less than, and certainly has never exceeded, the consultation blood pressure in the clinic prior to admission. The follow-up pressure readings are obtained in the clinic, the first with the patient sitting and the second with the patient standing for three minutes.

Electrocardiographic examinations. Many patients early in the surgical series had standard leads only. but later cases in the surgical series and

all those in the medical series were examined in addition to the standard leads, by augmented unipolar limb leads and the chest leads V_1, V_3 and V_6. These have been read to establish the existence of left ventricular hypertrophy. The paper of Sokolow and Lyon has been used as a standard in the interpretation of the tracings. Tracings have been repeated in all patients followed up.

Chest Radiographs. Six-foot chest films were taken in all cases and repeated at follow-up. Where comparable films are available, assessment of change in heart size has been made independently by the consultant radiologist and without the provision of clinical details.

Ophthalmoscopic examinations. These have been made by the consultant ophthalmologist who conducted follow-up examinations in the majority of patients.

Other investigations. Intravenous pyelography was carried out in all cases, in addition to blood urea estimation, urine concentration and dilution tests, Van Slyke urea clearance tests and microscopic examinations of the urine. In selected cases, benzodioxane tests and, more recently rogitine tests have been employed to exclude phaeochromocytoma, and where they appeared to be positive, urine was examined by bio-assay

in the University College Hospital, by the courtesy of Professor Rosenheim.

Grading of cases. In order to assess prognosis in comparison with published figures, classification of the patients into groups is necessary.

The choice of classification has been carefully considered in the previous section and the system of Keith is employed to group the patients in both series.

In each series a number of patients remain ungrouped and are listed as such. They comprise those patients with retainal grading 1 or 2, in whom serious functional derangement of heart, brain or kidney excludes them from the appropriate Keith groups.

SURGICAL SERIES.

Methods.

Four types of sympathectomy were employed, all two-stage operations.

1. Infradiaphragmatic Sympathectomy.

Beginning in September 1946, the first four patients were treated by this procedure, first developed by Adson and Allen. It involves, in two stages, bilateral resection of 1st and 2nd lumbar sympathetic ganglia, greater, lesser and least splanchnic nerves and the coeliac ganglia. Part of the coeliac plexus was also removed at each operation.

2. Extended Lumbar Sympathectomy.

The next five patients had this operation , in two stages. Removal of the twelfth rib allowed extension of the sympathectomy above the diaphragm and section of D.11 and D.12 ganglia was done in addition to the nerves sectioned in the solely infradiaphragmatic sympathectomy.

3. Thoraco-Lumbar Sympathectomy.

In June,1947, the earlier technique was replaced by this operation. Originally developed by Smithwick, it involved removal of the twelfth rib. In some of these patients the eleventh rib has been resected. The approach in the thorax is

retro-pleural and allows section of the sympathetic chain up to D.8 or D.7. The section was extended downwards to include L.2, the splanchnic nerves, and part of the coeliac plexus, by a transdiaphragmatic, retro-peritoneal approach. In some cases however, the removal of part of the coeliac plexus was omitted.

30 patients had this operation in two stages.

4. Extended Thoraco-Lumbar Sympathectomy.

In June, 1950, further extension of the sympathectomy was adopted as the standard procedure. By means of a transthoracic intra-pleural approach, section of the sympathetic chain up to the level of D.5, D.4 or even D.3 was achieved. The section was extended downwards to include L.1 or L.2. In only one patient in this group was there mention in the operation notes of section of coeliac ganglia or plexus.

25 patients had this extended sympathectomy in two stages.

Description.

The 64 patients in the surgical series have been graded according to Keith, and those patients fulfilling his criteria for groups 1 - IV are as follows:

	Females.	Males.	Total.
Group I	2	2	4
II	33	8	41
III	5	1	6
IV	2	3	5
	42	14	56

The remaining 8 patients (7 in retinal grade 2 and 1 in retinal grade 1) are excluded from groups I and II by reason of arterio-sclerotic complications of hypertension, and are recorded by sexes immediately below as ungrouped. The surgical series then comprises:

	Females.	Males.	Total.
(From above).	42	14	56
Ungrouped.	5	3	8
	47	17	64

Age and Diastolic Blood Pressure Levels.

The average age and the range, of the patients in each group, by sexes, is tabled, with the mean diastolic blood pressure in mms. of mercury and the range.

	No.	Females. Age in years. Mean.	Range.	Diastolic B.P. in mms.Hg. Mean.	Range.
Group I	2	26	(23 & 28)	130	(120 & 140)
II	33	44	(29 - 57)	140	(110 - 170)
III	5	42	(34 - 47)	155	(130 - 170)
IV	2	44	(38 & 49)	165	(155 & 175)
Ungrouped	5	49	(41 - 56)	131	(115 - 160)
		Males.			
Group I	2	44	(40 & 48)	125	(110 & 140)
II	8	43	(37 - 49)	134	(115 - 160)
III	1	33		130	
IV	3	44	(37 - 50)	145	(140 - 156)
Ungrouped	3	48	(47 - 49)	140	(130 - 160)

In the tables, notwithstanding the small numbers in each group, certain general trends are visible. The youngest patient at the time of operation was 23, the oldest 57 years. The mean age shows no tendency to rise from group I - group IV. In Keith's original series, with the sexes combined, the mean ages were 55, 41, 42 and 40 for groups I, II, III and IV respectively.

The mean diastolic blood pressures show a rise from group I - group IV for each sex, with the sole exception of the one male group III patient, and the average pressure is seen to be higher in the females. This latter finding is not unexpected, in that females appear to tolerate higher individual blood pressures than their male counterparts. In the grading of the patients, blood pressure levels were considered only in separating groups I and II, and so the successive rises in mean blood pressure levels in groups II, III and IV lend authenticity to the grading. The single exception to this trend is mentioned above. An interesting observation is the mean age scored by the eight patients exhibiting arteriosclerotic manifestations of hypertension - 49 years in the females, 48 years in the males. The levels are higher than in any of the groups in either sex, and are higher, in fact, than those of any group in Keith's original series, with the exception of the fifty-five years

in his own group I. Their age scores may be taken to suggest that arteriosclerotic complications occur only in longer-standing hypertension, and/or in hypertension of a milder tempo. The mean diastolic pressure scores of 131 and 140 in females and males respectively may favour the second possibility, but if any trends may be indicated by so few cases - these figures seem to cast doubt on the wisdom of classifications which upgrade on the basis of these complications.

Symptoms and Signs in the Surgical Series.

A summary of the chief symptoms and clinical findings shows the number of patients who at their first examination complained of the symptoms listed. The sexes are combined.

Headache -	Hypertensive type	24	
	Migraine	2	
	Other	31	
Headache -	All types		57
Exertional dyspnoea			43
Dizziness			18
Tiredness			15
Nervousness			3
Palpitation			3
Chest pain not truly anginal			5
Ankle swelling			5
Blurred vision			5
Epistaxis			1
Rotational vertigo			1

The migraine headache complained of in two patients, is included in the total for it will be later recorded that this symptom disappeared with the operations. (In two other patients, migraine has

not been listed above, because although it had been present since childhood it had been replaced subsequently by a different type of headache, having the characteristics of a typically hypertensive headache).

The significance of the symptom of chest pain, which was not related strictly to effort, was doubted until the symptom was elicited at first hand in several patients in the medical series. Further, it returned as one of the first indications of relapse in two of the surgical patients.

These symptoms are the totals complained of in the surgical series. Some of these patients however exhibited clinical features of major disorder in heart, brain or renal function which excluded them from Keith's groups I and II if the retinal grading would otherwise place them in these groups. These features are:-

Congestive Cardiac Failure.

Recent congestive cardiac failure had occurred in two patients, and in one of them the presence of nocturnal dyspnoea is taken to mean left as well as right heart failure.

Cerebro-vascular Accident.

There was a history of cerebro-vascular accident in six patients - four of them had cerebral thromboses; in three patients this had occurred twice and two had subarachnoid haemorrhage.

Impaired Renal Function.

Albuminuria - Two patients showed albuminuria in excess of a trace, with no other evidence of renal damage.

Raised Blood Urea. - One patient only, had a raised blood urea with marked albuminuria.

Renal Function Tests. - In many patients the results of the urea clearance tests were between 50% and 75% of average normal, a range usually regarded as of doubtful significance. In these patients, however, intravenous pyelograms, urine concentration and dilution tests, urine microscopy and clinical history did not suggest renal functional impairment, and normal function has been assumed.

Peptic Ulcer History.

Three patients had had a haematemesis and in two of them and in a further two patients, there was a past history of peptic ulcer. One patient gave a history of melaena.

Abnormal Pregnancy History.

The abnormalities that concern us are:

1. Hypertension complicating pregnancy, a condition which might be covered by the term pre-eclamptic toxaemia, or more precisely, specific hypertensive disease of pregnancy.

2. Pregnancy occurring on the basis of a pre-existing hypertension, with the possible supervention of symptoms of toxaemia.

Records are not available to separate accurately these two conditions in the patients in this series, but evidence of hypertension which was discovered for the first time in the later months of pregnancy from six months onwards, has caused the patients showing it to be grouped under 1, and where records reveal hypertension in the early months this has caused these patients to be grouped under 2.

33 women in the surgical series gave a history of one or more pregnancies. In 17 women there was no mention of toxaemia or hypertension and in a total of 56 pregnancies, 44 live infants resulted. There were 7 miscarriages and 5 still-births. In the remaining 16 women there was a history of toxaemia or hypertension or ankle swelling or severe vomiting in one or more of their pregnancies. In a total of 40 pregnancies 19 live infants were produced.

This second group of 16 women is of interest to us in this paper and the details of their pregnancy histories are as follows, grouped under the headings explained above:-

1. Pre-eclamptic toxaemia. This appeared in

11 women who in 35 pregnancies, gave a history of:-

Eclampsia in 1.
Pre-eclamptic toxaemia in 14 pregnancies - 2 live infants.
Miscarriages in 8.
Normal pregnancies in 12.

2. Pre-existing hypertension. There was evidence of this in three women, details of whom are as follows:-

One patient was operated on during pregnancy.
One had caesarean section, but lost the child.
One successfully carried through the pregnancy.

In addition one patient complained of severe vomiting during pregnancy.
One patient complained of severe ankle swelling during pregnancy.

Chest Radiographs.

In the assessment of heart size the chest films were studied and graded for evidence of left ventricular hypertrophy as none, slight, moderate and marked.

		Enlargement.			
Surgical Series.	No Film.	None.	Slight.	Moderate.	Marked.
64 patients.	3	18	19	20	4

Thus in 61 available films, 43 patients in the surgical series show radiological evidence of left ventricular hypertrophy.

Electrocardiographs.

In the assessment of evidence of left ventricular hypertrophy in the electrocardiographic tracings, using as a standard, the findings of

Sokolow and Lyon, the records have been graded with particular reference to the RST and Twave changes in the standard, augmented unipolar and praecordial leads. The grades are none, denoting no change, (1) minimal, (2) moderate and (3) marked, assessed by comparison with the patterns illustrated.

Sokolow and Lyon were also able to deduce the presence of left ventricular hypertrophy, in the absence of RST - T wave change, if one or more of the following features were present in the electrocardiographic tracings.

i. The measurement of R_1 and S_3 was 25 mms. or more.
ii. The measurement of S in V_1, and R in V_5 or V_6 exceeded 35 mms.
iii. The onset of the intrinsicoid deflection in V_5 or V_6 exceeded 0.06 seconds.

These measurements were made in all the records examined, but in no cases in either series were any or all of these changes present, in the absence of RST - T wave changes and so the records were graded, as explained above entirely on the basis of the latter changes.

The findings at the first examination, appropriately graded are listed as follows:

		Left Ventricular Hypertrophy.			
Surgical Series.	No Tracing.	None.	Minimal.	Moderate.	Marked.
64 patients.	2	19	15	12	16

Thus from the 62 available tracings, in 43 was found evidence taken to indicate left ventricular hypertrophy.

Ophthalmoscopic Reports.

The grouping of cases has been on the basis of the ophthalmologist's report on the retinal findings prior to operation.

In 61 of the 64 patients, detailed reports allow the following descriptions of the retinal picture to be itemised.

mild sclerosis	4
+ primary sclerosis	3
arteriosclerotic retinopathy	0
attenuation	9
attenuation & mild sclerosis	12
++ attenuation, spasm, mild sclerosis	16
+++ hypertensive retina with marked sclerosis	6
hypertensive retinopathy	6
papilloedema	5
	61

+ The term primary sclerosis has been applied to eye grounds which in the opinion of the ophthalmologist, represent a picture of pure arteriosclerosis, and in which, in his opinion, the existence of hypertension is likely to be incidental. This designation figures more prominently in the ophthalmoscopic reports on the medical series, and in the follow-up of the medical series it appears to provide some interesting correlations in the clinical features and therapy.

++ The use of the term spasm and the actual existence of the changes it is meant to describe have been closely questioned by Pickering (1956). The writer is not qualified to join issue on this point, but the term as employed here describes a localised narrowing in the retinal arterioles of a temporary nature. The disappearance of spasm has been observed in a number of cases by the ophthalmologist and these instances are recorded in the follow-up.

+++ Hypertensive retina; a term used to described a typical retinal picture of hypertension, i.e. generalised narrowing of the arterioles, concealment at crossings, arterio-venous kinking. One patient admitted to hospital following a sub-arachnoid haemorrhage, exhibited papilloedema, the rapid subsidence of which in the absence of blood pressure alteration, and in the absence of haemorrhages and exudates, established the retinal grade as 2 and not 4.

Since these reports form the basis of the grouping, the distribution by groups is tabulated.

Keith Groups.	Mld. Scl.	Prim. Scl.	A/S Rt. pthy.	Attn.	Attn. & Mild Scl.	Attn. Spm. & Mld. Scl.	Ht. Rt. & Mkd. Scl.	Ht. Rt. pthy.	Pda.
I				1		2			
II	4	2		7	11	13	3		
III								5	
IV									5
Ungrouped		1		1	1	1	3		

Scl. - sclerosis. Attn. - attenuation.
Ht.- hypertensive. Pda. - papilloedema.

It will be noted that in two cases, retinal findings of attenuation, spasm and mild sclerosis occur in group I. This grouping is made on the basis of the clinical state which from Keith's instructions may overrule the strict retinal grading. Absence of symptoms and liability of blood pressure dictated the classification.

Results in the Surgical Series.

Survival.

In a 2 - 10 year follow-up of the 64 patients, 20 have died.

Group II	- 8	-	20% mortality.
Group III	- 3	-	50% mortality.
Group IV	- 5	-	100% mortality.
Ungrouped.	- 4	-	50% mortality.

Deaths.

Group II - 8 deaths.

F.41. Survival 0. - Complained of rotational vertigo, tinnitus and nausea - no other symptoms. Died of massive pulmonary collapse at second operation. - Severe coronary atheroma at P.M.

M.37. Survival 6 years. - Hypertensive headaches for 4 years before operation. Good hypotensive effect for 1½ years, with relief of symptoms. Symptoms and hypertension returned, to be partially controlled with small doses of oral vegolysen. Cause of death - uraemia.

M.38. Survival 8¾ years. Complained of headaches for 10 years. Albumin in urine, blood urea 52 mgms.%. Good hypotensive effect for 2 years. Cause of death - uraemia.

M.43. Survival 1¾ years. 4 years of occipital headaches and moderate exertional dyspnoea. Normotensive with loss of headaches for 9 months after operation, then diplopia. Cause of death severe coronary arteriosclerosis.

M.45. Survival 8¾ years. Complaint of sleeplessness and irritability. No effect on blood pressure - but subjective improvement. Hemiplegia after 2 years, and again after 6 years, and died of cerebro-vascular accident.

F.48. Survival 2½ years. Complaint of hypertensive headache; fundi - generalised attenuation with one small patch of exudate. Good blood pressure response. Clinical improvement for 1 year then had 3 subarachnoid haemorrhages after operation. Cause of death - coronary thrombosis.

F.38. Survival 3 years. Complained of hypertensive headaches. High blood pressure discovered in first pregnancy 9 years before. Slight temporary reduction in blood pressure. Death presumed since no trace after 3 years.

F.44. Survival 4½ years. Symptoms included moderate angina of effort. Experienced slight subjective improvement, but no alteration in blood pressure. Died suddenly-cause unknown.

Group III. - 3 deaths.

F.34. Survival 2¼ years. No effect on blood pressure - slight subjective improvement. Cause of death - cerebral haemorrhage.

F.41. Survival 4¾ years. History of 2 years headache. No effect on blood pressure or symptoms. Cause of death - cerebro-vascular accident.

M.44. Survival 1 year. History of 1 year's headache, exertional dyspnoea, recent blurring of vision and substernal pain for 1 day. Subjective improvement, but no effect on blood pressure. Died - cerebro-vascular accident.

Group IV. - 5 deaths.

F.49. Survival 2 years. Good blood pressure response and relief of headache for 1 year, but return of headaches. Death - suicidal drowning.

F.38. Survival 7 months. Immediate relief of headaches, but 3 months after operation onset of uraemia and blood pressure 270/210. No P.M.

M.49. Survival 1½ years. No subjective or objective improvement. Cause of death unknown.

M.46. Survival 4 years. Complaint of severe headache, dyspnoea for 2 years. Some improvement in blood pressure, but subjective improvement considerable (Won M.B.E. during East Coast floods). Oral hexamethonium bromide added with no alteration in blood pressure. Intra-muscular injections in last few months partially effective. Cause of death - uraemia.

M.37. Survival 1¼ years. Headaches 3 - 4 years. Recent blurring of vision. Good hypotensive effect and returned to active farming. Cause of death - cerebral haemorrhage.

Ungrouped - 4 deaths.

M.48. Survival 3 years. Had had 2 attacks of aphasia with facial palsy and headaches in previous year. Symptoms cleared and good response in blood pressure till he died of posterior inferior cerebellar artery thrombosis.

F.56. Survival 3 years. Headache and 2 cerebro-vascular accidents before operation - good hypotensive effect, but poor subjective result - marked weakness and lethargy. Cause of death unknown.

F.49. Survival 1½ years. Complaint of headaches - 2 years. Cerebral thrombosis and subarachnoid haemorrhage in year prior to operation. Good blood pressure response, but little subjective improvement. Cause of death - cerebral haemorrhage.

F.52. Survival 10 months. 10 years before, mild cerebro-vascular attack, 2 years before - hemiplegia following a stroke, headaches - 1 month. No effect on blood pressure by operation. Cause of death - cerebral thrombosis.

In at least 8 of the 20 patients who died, the operations achieved a satisfactory reduction in blood pressure with concomitant clinical improvement, for varying periods. In a further 5 patients in spite of the absence of hypotensive effect, subjective improvement was achieved. In 6 patients the operations were a complete failure, and one patient died a few hours after the second operation - the only operative death in the 64 patients.

Effect on Prognosis.

42 patients in the surgical series grouped strictly according to Keith, were operated on, 5 or more years ago. To assess the effect of surgery on the prognosis, yearly death rates up to 5 years, have been calculated for the patients in the appropriate groups, and, expressed as percentages, are grouped as follows:-

Death at Yearly Intervals after Operation, expressed as percentage.

(Present Series 5 years).

		Years.				
Group.	No.	1st.	2nd.	3rd.	4th.	5th.
I	1	0%	0%	0%	0%	0%
II	31	3%	6%	13%	16%	16%
III	5	0%	20%	40%	40%	64%
IV	5	20%	60%	80%	80%	100%

These figures are now compared with those published by Keith Wagener and Barker (1939) for the yearly death rate percentage of 219 patients, treated with rest, diet and sedatives and without specific therapy. They are reproduced below and illustrated in graph 1.

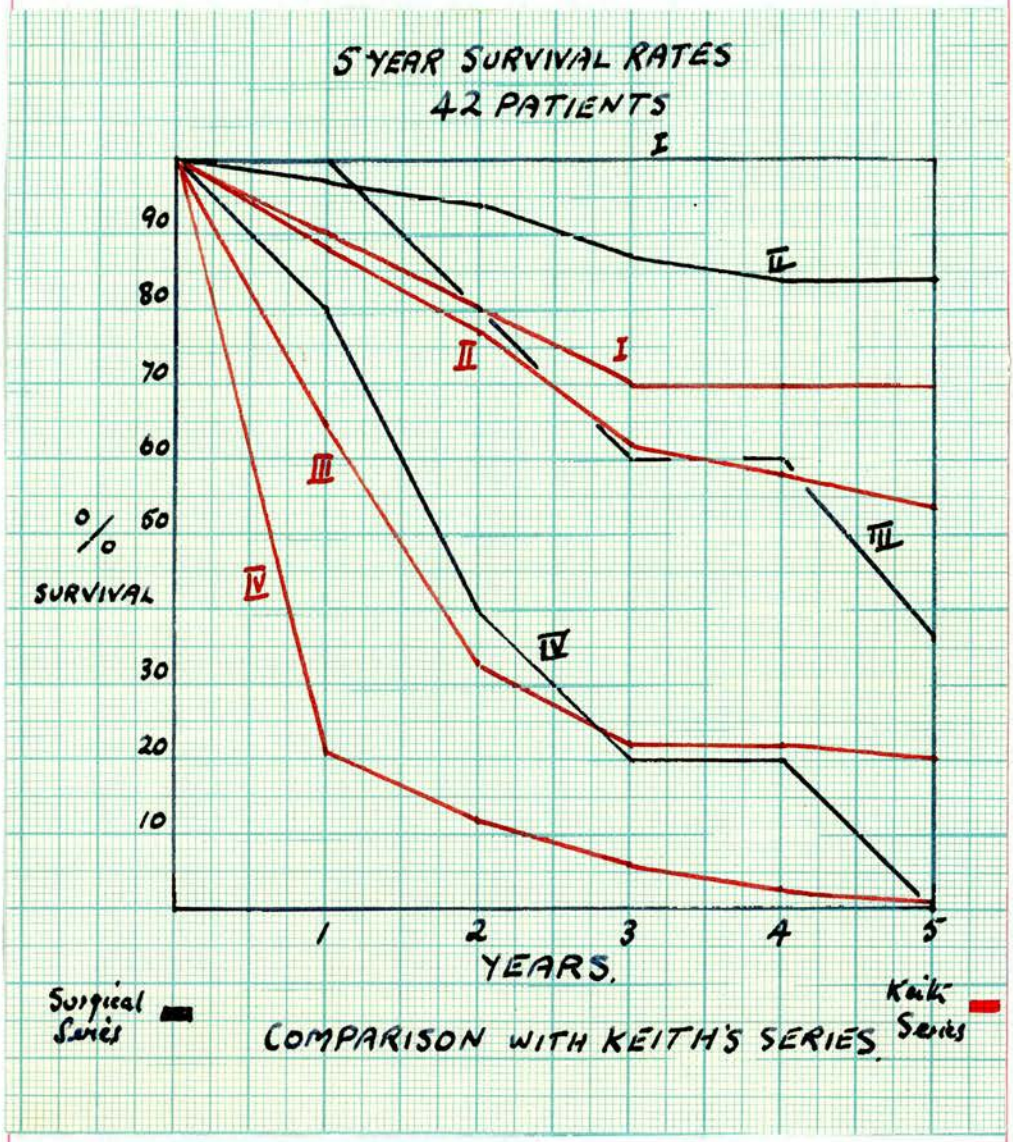
Death at Yearly Intervals after First Examination. (Expressed as percentage).

+
(Keith 5 years).

		Years.				
Group.	No.	1st.	2nd.	3rd.	4th.	5th.
I	10	10%	20%	30%	30%	30%
II	26	12%	23%	38%	42%	46%
III	37	35%	67%	78%	78%	80%
IV	146	79%	88%	94%	98%	99%

+ Keith et al. Amer.J.Med.Scl.197;332,1939.

GRAPH 1.



Effect on Prognosis.

Present Surgical Series.

Group.	No.
I	1
II	31
III	5
IV	5

Keith's Series.

Group.	No.
I	10
II	26
III	37
IV	146

From comparison of the two tables it is seen that in group II the mortality rate is reduced in the operated cases at 5 years with 16% as against 46%.

The numbers in the other groups are too small to allow firm comparisons to be made, but in groups III and IV the mortality rate is at each stage lower than the figure for Keith's cases.

The surgical improvement on prognosis is now compared with figures for mortality rates at 5 years published by Smithwick, 1951.

Surgical Series Smithwick.+ Keith Groups.			Present Series. Keith Groups.		
Group.	No. of cases.	Mortality at 5yrs.%.	Group.	No. of cases.	Mortality at 5yrs.%
I	165	10.3	I	1	0
II	142	16.9	II	31	16
III	154	34.5	III	5	60
IV	77	49.5	IV	5	100

From the comparison of these two tables it is seen that the results in group II in this series are almost identical with those of Smithwick and the parallelism is accepted as confirming the advantages of surgical treatment, but more important to the present study, it is accepted as confirming the authenticity of the grouping as applied here.

As stated in the introduction, one of the main objects of presenting a series of patients

+ Smithwick, R.H., J.A.M.A. 147: 1611, 1951.

treated by an approach, now only rarely employed, was to provide a standard. An attempt has now been made to establish the surgical series in relation to published work by means of these prognostic comparisons with Keith's series and with Smithwick's series.

Much of the present study will lose its point if I have failed to establish this relationship. The medical series will still have a standard for comparison, but may not be related, through the surgical series, to the long follow-up studies available in the literature.

In consequence, comparative studies of the effects of treatment in the two series, in the early stages, will not allow any conclusions, relative to the probable effect on prognosis of the medical series.

Since improvement in prognosis is the only undisputed means of assessing the effect of therapy in hypertension, the inability to outline the expected course for the medical series would detract from the value of the present study.

These remarks are applied to group II since the patients in the other 3 groups are too small to make any valid comparisons.

Originally groups I and III were larger, since I included a further 8 patients who exhibited

arteriosclerotic complications of hypertension, but after careful reading and examination of the system of classification and a personal communication (Keith) these patients were excluded to ensure faithful interpretation of criteria for classification.

The Effect of Surgical Treatment on Blood Pressure.

In assessing the effectiveness of control of the blood pressure, two readings are compared, the initial diastolic pressure and the follow-up diastolic pressure. The conditions adopted in obtaining these readings were described in the introduction. In addition, at the follow-up, if the diastolic pressure obtained with the patient standing (recorded at the end of 3 minutes) was less than that obtained with the patient sitting, the lower reading has been accepted as the follow-up value. This proviso is adopted to ensure the recording of hypotensive effect which requires the upright posture to reveal its presence.

The readings themselves are casual readings, but it is confidently claimed that the pressures recorded fairly represent the pre-operative and follow-up levels, since the readings which form the basis of the following calculations have the support of similar values obtained at numerous

attendances in the out-patient department, and in the family practitioner's surgery.

Grading of Response.

A comparison made between the initial blood pressure reading taken at the first formal examination after admission, and the follow-up reading, determined the grading of response, calculated as follows:-

Good Response occurred when there was a drop of 20 mms. or more in the level of the diastolic pressure provided that the follow-up reading was 110 mms. of mercury or less.

Poor Response occurred when there was a drop of 20 mms. or more in the level of the diastolic pressure if the follow-up reading was over 110 mms., but did not exceed 125 mms.

Failed Response was recorded if no response occurred or if, in spite of a drop of 20 mms. or more in the level of diastolic pressure, the follow-up reading was still in excess of 125 mms. of mercury.

Effective Blood Pressure Control - 6 months after operation.

This period was chosen, because it allows comparison to be made with the medical series which has been followed-up for six months or more.

When the criteria outlined in the above paragraph were adopted, it was found in the survey

of the blood pressure responses of the 64 patients in the surgical series, that 32 patients or 50% showed good blood pressure response six months after operation, that is -

SURGICAL SERIES - 50% EFFECTIVE B.P. CONTROL AT 6 MONTHS.

A 50% success rate at six months, in blood pressure control represents, by comparison with published results, a not unusual achievement.

For example Fishberg (1948) followed up forty patients of various surgeons and at thirteen to twenty-four months, the figure for the proportion of significant blood pressure reduction was 56%.

While different writers provide various percentages for initial success in controlling the blood pressure, there is however, unanimous agreement that a considerable proportion relapse, and moreover Fishberg (1954) and Pickering (1957) imply that this loss of effect is gradual. A study of the maintenance of blood pressure control in the present surgical series will throw light on this point.

Pattern of Blood Pressure Control in the Surgical

In the examination of this problem the surgical series has been split up into a number of follow-up groups, depending upon the time since the second operation.

The length of the follow-up, the number of

patients in the follow-up, the good responses in each follow-up group expressed as a percentage of the number in that group, together with the percentage of deaths in each group, are tabulated.

It must be emphasised that the tables show isolated groups and do not represent a continuous series with the exception of the first three columns, in which the totals followed are identical.

Good response implies again, a drop of 20 mms. or more in the diastolic pressure to 110 mms. of mercury or below.

Blood Pressure Response. Surgical Series. Isolated Groups.

Patients.	64	64	64	63	61	60	49	42	28	18
Follow-up	Months. 3	6	1	2	3	Years. 4	5	6	7	8
% Good Response.	56	50	47	46	41	28	26	24	22	28
% Deaths.	2	3	8	16	21	25	35	36	32	32

It is seen from this table that the percentage of good responses appears to remain fairly stable in the 1, 2 and 3 year follow-ups, viz. 47%, 46% and 41% respectively. The suggestion of a falling off in response at 3 years is accentuated in the 4 year follow-up with a percentage of 28. Thereafter, in the successive groups, the good response grading showing a continuing reduction, but at 8 years the figure is

again 28%.

The general conclusions suggested by these isolated groups are that the longer the follow-up period, the smaller the percentage of good responses. The figures do not suggest gradually diminishing dividends however, but a sudden drop in effectiveness in the early months after operation, then comparative stability for two to three years, next a steep drop in effectiveness to the fourth year, followed by several years when no major change is indicated.

These trends can only be suggested by figures for isolated groups and the period which merits close study is at four years and after. The series does not provide a sufficient number of cases to justify a useful 8-year follow-up study, but blood pressure records are available for a 5-year study. Therefore to obviate any fallacies that may arise from the different composition of the isolated follow-up groups, 49 patients with blood pressure records spanning 5 post-operative years, have been graded with reference to blood pressure response as described. The grades achieved at each of the following intervals after operation have been calculated - 3 months, 6 months, 1 year and then every year up to 5 years. In each column, the percentages of good, poor and failed responses have been tabulated at the successive

intervals following operation, and the percentage of deaths recorded.

Blood Pressure Responses in 49 patient followed over a period of 5 years.

	Time after operation.						
	Months.				Years.		
	3	6	1	2	3	4	5
Good Responses.%.	61	53	47	45	39	26	26
Poor Responses.%.	8	10	6	6	4	10	10
Failed Responses.%.	37	45	43	35	35	43	39
Deaths.%.	2	4	10	20	26	31	35

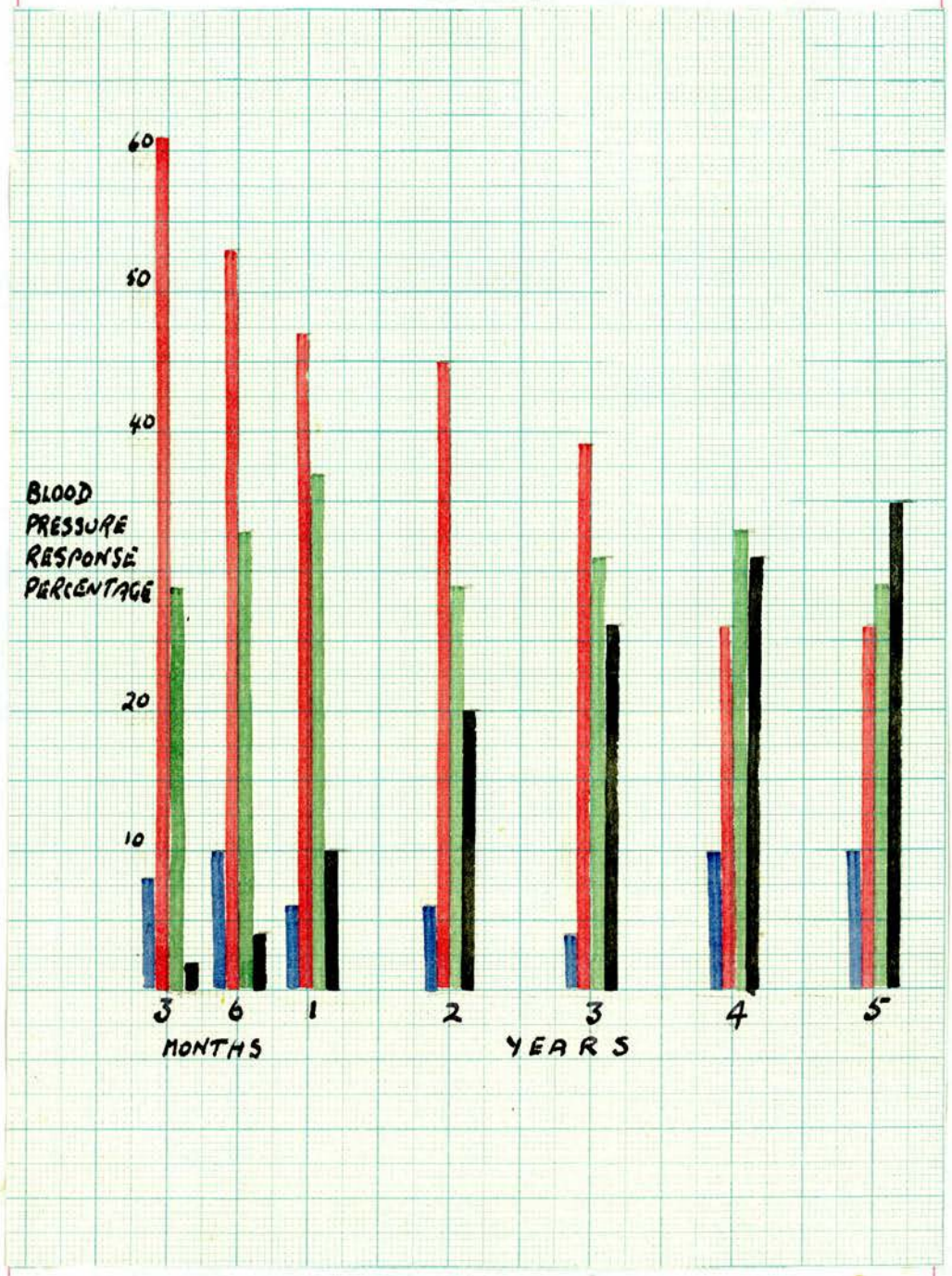
See Graph 2.

These figures and the graph indicate a pattern of response which had been anticipated from the results in the isolated follow-up groups.

Effective control of blood pressure, indicated by the percentage of good responses, falls sharply in the first few months after operation and then falls more slowly to the end of the second year. The fall now begins to accelerate and the greatest single drop occurs between the third and fourth years, but then, no further loss of effect is indicated by the percentage for the fifth year.

It can also be observed from the figures that a rise in the death rate coincides with a fall in poor response and failures, but does not coincide with a fall in the successes, thus implying that the deaths came from the poor responses or failures.

GRAPH 2.



Blood Pressure Responses in 49 patients followed over a period of 5 years.

Columns indicate percentage response in diastolic blood pressure,
Red - Good Response. Blue - Poor Response,
Green - Failed Response, Black - Deaths, at the time interval after operation indicated.

Thus the value of controlling the blood pressure would seem to be established.

A final observation, that a fall in the percentage of well controlled cases is accompanied by an equivalent rise in the percentage of poor responses and failures, allows us to infer that though loss of control does not immediately result in an increased death rate, it will ultimately do so, for it raises the percentage of poor responses and failures, and this group is seen to be vulnerable in respect of mortality.

The Effect of Surgical Treatment on Symptoms.

Headache.

In the whole surgical series of 64 patients, 57 complained of headache. Following operation:-

35 had complete relief. (62%).
11 had improvement in headache. (19%).

SURGICAL SERIES - 81% RELIEF OR IMPROVEMENT IN HEADACHES.

The success of the operation in the relief of headache is a general experience and most published series give similar results. In a series of patients referred for surgery, Fishberg, 1948, found that 64 (77%) of 83 patients complaining of severe headache, experienced complete or almost complete relief following operation.

In a number of the patients in this series, relief of headache has not been permanent, and in 14 the headaches have returned after an interval varying from 3 months to 5 years, the average period being 2½ years.

Exertional Dyspnoea.

This symptom was noted pre-operatively in 43 patients.

14 claimed improvement following operation, (33%).
24 noticed no change. (56%).
5 noticed a continued deterioration in exercise tolerance. (11%).

SURGICAL SERIES - 33% IMPROVEMENT IN DYSPNOEA.

In addition, one patient experienced dyspnoea on exertion for the first time after operation.

These data were obtained in a survey conducted one to six years after the operations.

In a second survey, after a lapse of four years, impaired exercise tolerance was noted for the first time in 6 patients and further impairment was noted in 15, in whom temporary improvement for three to five years, had followed operation.

In this second survey, it was recorded that 4 patients had evidence of incipient congestive cardiac failure and were requiring regular injections of mercurial diuretic.

It was also noted that 2 patients who had

had incidents of congestive failure immediately prior to operation were alive and well, eight and ten years later respectively.

Radiological evidence of Alteration in Heart Size.

The radiologist conducted a survey, involving comparison of pre-operative films and of post-operative chest films taken one to five years later, with the object of assessing change in heart size. Comparable films were available in 36 patients.

28 of these showed evidence of left ventricular hypertrophy before operation.

13 showed a reduction in heart size in films on average, 3 years after operation. (46%).
2 became larger. (8%).
13 were unchanged. (46%).

SURGICAL SERIES - 46% REDUCTION IN HEART SIZE.

8 showed no evidence of hypertrophy in pre-operative films.

After operation:-

5 of these remained unchanged.
3 showed evidence of hypertrophy.

A further survey 4 years later enabled comparisons to be made in 19 of the original 36 patients.

Interesting findings were:-

In the 13 patients who had shown reduction in heart

size in the first survey -

8 maintained this reduction for an average of six and a half years to date.
2 have shown again increase in size.
3 films were not available for comparison.

In 6 other patients the second survey showed, for the first time, increase in heart size.

Electrocardiographic Records following operation.

Tracings before and after operation were available in 46 patients.

Hypertrophy was present before operation in 30 records:

15 post-operative records showed improvement (50%).
8 post-operative records showed no change.
7 post-operative records showed deterioration.

SURGICAL SERIES - 50% IMPROVEMENT IN ELECTROCARDIOGRAPHS.

In those showing improvement, 12 showed reduction in grade (see initial criteria p.45 and 3 showed improvement but not downgrading, Further, the initial improvement was maintained in 7 to date or death in 5 - 8 years, but regression was seen to occur in the remaining 8, at varying periods from 1 - 5 years.

In the 16 patients with no initial abnormality pre-operatively -

12 remained normal post operatively, and
4 showed evidence of left ventricular preponderance for the first time.

Ophthalmoscopic Follow-up Surgical Series.

Follow-up examinations were conducted in 39 patients and the initial categories with the post-operative reports are recorded.

Attenuation in 3 - relieved in 1.
Attenuation and mild sclerosis in 9 - attenuation lost in 1, less in 2, sclerosis increased in 3.
Mild sclerosis in 2 - increased in 1.
Primary sclerosis in 2 - increased in 2.
Attenuation, spasm and mild sclerosis in 14 - spasm lost in 8; attenuation lost in 4.
Hypertensive retina with marked sclerosis in 3 - marked attenuation remains in 2.
Retinopathy in 5 - cleared in 4.
Papilloedema in 2 - lessened but did not clear in 2.

To summarise the above, it will be seen that reversible changes in the retina, attenuation, spasm, retinopathy and papilloedema were present in 36, and improvement occurred in 23 (64%).

SURGICAL SERIES - 64% OPHTHALMOSCOPIC IMPROVEMENT.

The Successes and Failures in the Surgical Series.

From the post-operative records of blood pressure levels, extending in some patients over a period of ten years, it is possible to classify the individual patients as successes or failures with regard to control of diastolic blood pressure.

24 are failures, including those patients in whom a transient fall in diastolic blood pressure, lasting a few days to a few weeks, was achieved, but in whom it was not maintained for as long as 6 months.

4 patients achieved partial control i.e. poor response following operation.

16 patients achieved and maintained good response of blood pressure for at least 6 months after operation, but then relapsed, with return of blood pressure to pre-operative hypertensive levels. This relapse in the majority, was an easily recognised clinical entity, occurring over a period of a few weeks, and the return of symptoms usually heralded the discovery of the raised blood pressure. The most frequent time for relapse to occur was between two and a half and three and a half years after operation. In only one patient has relapse occurred later than four years after the operation and this took place after an interval of six years.

20 patients have achieved and maintained good response in diastolic blood pressure levels to date or to death.

The death of a patient after a considerable period of good control has been classified as a success. In fact 3 of these 20 patients have died, after successful blood pressure control (and clinical improvement) for nine months, one year and two and a half years. The remaining 17 (except for one operated on over three and a half years ago) have been followed up for over four years and maintain good control.

Thus at approximately four years, 17 out of 64 or 26% are successfully controlled.

At page 60 et seq. the percentage of effective blood pressure levels (i.e. good responses) has already been calculated for 49 patients at four years and five years and the figure was also 26%. The corresponding figure for 18 patients followed up for eight years was 28%. If it be accepted that as already suggested relapse is rare after four years, it seems reasonable to expect that the score of successful results at the end of eight years for the surgical series, will not be much below 26%, in the absence of deaths in these well-controlled patients.

The addition of the 16 temporary successes to these 17 permanent successes provides 33 (or

51%) of successes at the outset, thus approximating to the figure of 53% at six months, already tabled in the 5 year follow-up group, (page 60).

In respect of blood pressure control we can thus expect after six months approximately 50% successes. After four years the figure has dropped to 26%, when all the temporary successes have relapsed.

The success rate for this series at four and five years has been calculated at 26%, but this figure gains confirmation from other series. Whitelaw and Smithwick, 1951, find marked lowering of the diastolic pressure (20 points or more are specified) in 27.7% of 85 cases after five years. Palmer, 1947, reported 25% of 68 patients to have normal or near normal blood pressures after three years. (Smithwick was again the surgeon in the second series quoted).

Correlation of Successes and Failures.

Certain correlations of these successes and failures in respect of blood pressure control are now studied.

Correlation with Keith's Groups.

The distribution, in the appropriate Keith groups, of the various categories in control of blood pressure, allows us to calculate the proportion of successes, temporary successes, partial successes

and failures in each group.

A table showing the percentage of successes and temporary successes in each group, is reproduced below.

		Percentage.	
Group.	No.	Successes.	Temporary Successes.
I	4	50%	25%
II	41	34%	32%
III	6	17%	16%
IV	5	20%	0%
Ungrouped	8	25%	13%

If we combine the percentages of permanent and temporary successes in each group we obtain percentages of initial success, that is, up to six months, for each group. We find then that initial success in the control of blood pressure was achieved in 75%, 66%, 33%, 20% and 38% in groups I, II, III, IV, and the ungrouped cases respectively. While the figures indicate a much higher success rate for groups I and II compared with the other groups, the few patients in the groups other than II make firm conclusions unwise. The fact however that of 41 patients in group II, 66% were initially successful, and 34% permanently successful, deserves emphasis.

Correlation with Type of Operation.

The operative procedure was now investigated in relation to the results. The number of patients dealt with by each procedure and the percentage of

successes, temporary successes, partial successes and failures are tabulated.

Sympathectomy Operation.	No.	Percentages. Success.	Temp. Success.	Partial Success.	Failure.
L.	4	50	25		25
Ext.L.	5	20	40		40
L.d.	30	20	33	10	37
Ext.L.d.	25	40	12	4	44

L - Lumbar.
Ext.L.- Extended Lumbar.
L.d.- Lumbo-dorsal.
Ext.L.d.- Extended Lumbo-dorsal.

4 patients following upper lumbar sympathectomies provided 3 initial successes, one of whom relapsed, while in 5 patients extended lumbar sympathectomies provided 3 initial successes, two of whom relapsed.

The remaining 55 patients in the surgical series were dealt with by one of two approaches, lumbo-dorsal sympathectomy and extended lumbo-dorsal sympathectomy. 30 patients were subjected to lumbo-dorsal sympathectomy and of these, 20% achieved permanent control and 33% temporary control. 25 patients were subjected to extended lumbo-dorsal sympathectomy and of these, 40% were permanently controlled and 12% achieved only temporary control. The initial success rate with these two approaches is similar, 53% and 52%, but a much higher proportion of cases are destined to relapse after lumbo-dorsal sympathectomy (33%) than after extended lumbo-dorsal sympathectomy (12%).

This difference invites explanation.

It has often been suggested that regrowth of the divided nerves is responsible for the high relapse rate in blood pressure control following sympathectomy. It is therefore of interest that McPherson and Kessel (1956) in a study of a group of patients with peripheral vascular disorders, reported that in these patients who had had a lumbar sympathectomy which was considered technically good, there ensued a lasting vaso-vilatation in the blood vessels of the feet.

The operations performed in the present surgical series were, without exception, reported to include bilateral removal of Lumbar ganglia 1 and 2, and in some cases, Lumbar 3.

> Reliable data, based on subjective experience, were available in eighteen patients only, to provide these observations. Nine experienced permanent (to date) warmth to feet previously cold, but at the same time, some complained that the slightest drop in temperature gave them now, cold hands, while two patients experienced permanent (to date) warmth in one leg only. Seven experienced no change.
>
> Of the eleven patients above in respect of blood pressure, four were successes, two were temporary successes, two were partial successes, and two were failures: of the seven patients above four were successes, one was a temporary success, and two were failures.

These observations illustrate that success in blood pressure control is unrelated to the production of vaso-dilatation in the feet. They are consonant however, with the opinion of

McPherson and Kessel, referred to above, that the effects of (adequate) lumbar sympathectomy are permanent. The explanation of the high relapse rate in blood pressure control following lumbo-dorsal sympathectomy, must be sought elsewhere.

Boyd and Monro (1949) drew attention to an 'escape' area with sudo-motor function still intact, after lumbo-dorsal sympathectomy. They suggested that failure to remove intermediate lumbar sympathetic ganglia, easily missed in the normal lumbo-dorsal sympathectomy, might be responsible for this escape area, involving sometimes the twelfth thoracic to the third lumbar dermatomes. Since these ganglia, however, were apparently without visceral connections and therefore not concerned in the nerve supply to the kidney or the splanchnic bed, failure to remove them is unlikely to be associated with relapse in blood pressure control.

The importance of complete denervation of the kidney and adrenal glands is stressed by D'Abreu (1953). This involves as complete an ablation as possible of the coeliac ganglion and its many filaments, the upper two lumbar ganglia and as well, complete removal of the splanchnic nerves, a sometimes difficult anatomical exercise.

In the light of these considerations, the

following tentative suggestions are made, to explain the different relapse rates in this series with the various techniques. In Lumbo-dorsal sympathectomy complete splanchnic denervation may not always be achieved in view of the technical difficulties involved and relapse may follow, if nerve regeneration occurs. Extension of sympathectomy to include T_5, T_4 or T_3 by making certain of the division of preganglionic fibres destined for the splanchnic nerves, ensures complete interruption of the latter, and relapse is rare. The restricted field in purely lumbar and splanchnic sympathectomy may have brought a measure of success to these early cases, by concentrating attention on those nerve pathways, interruption of which ensures success.

Two final points are worthy of mention. Firstly, a high relapse rate is a feature of all published results in lumbo-dorsal sympathectomy, not least in Smithwick's own cases. Palmer (1947) reporting on some of these cases with initial success of 66% in controlling the blood pressure, found that this percentage fell to 53% after one year, to 40% up to two years and to 25% after three years. The figures in the present series are almost identical.

Secondly, no matter how complete the

sympathectomy, there is a group of cases in which the operation is a complete failure. The more severe the hypertension (as judged by Keith's groups), the higher the proportion of failures.

Correlation with Clinical Features.

The improvements in symptoms and clinical features are now related to the results in relation to blood pressure control i.e. the successes, temporary successes and failures.

1. Headache.	Complete relief.	No relief.	Late return.
Successes.	88%	12%	
Temporary successes.	71%	7%	35% average 3 years.
Failures.	36%	32%	32% average 2 years.

2. Exertional Dyspnoea.	Improved.	Worse.
Successes.	36%	14%
Temporary successes.	56%	0
Failures.	19%	12%

3. Electrocardiograms.	Improved.	Worse.	Late return.
Successes.	33%	11%	11%
Temporary successes	64%	18%	45%
Failures	33%	45%	-

4. Chest X-Rays.	Heart Size. Smaller.	Larger.
Successes.	56%	-
Temporary successes.	50%	-
Failures.	38%	24%

5. Retinae.	Improved.
Successes.	70%
Temporary successes.	64%
Failures.	60%

A study of these correlations is interesting and shows the benefits conferred by successful surgery. The figures are based on the follow-up records available, where the initial state was capable of improvement by treatment, i.e. electrocardiographs showing hypertrophy, retinae showing potentially reversible changes.

It is seen that the improvements though more marked and more permanent in the successfully controlled patients, are not restricted to these patients alone.

Moreover, in the temporarily controlled cases, the return of headaches, initially relieved, and the later deterioration of electrocardiograms initially improved, underline the completeness of the relapse in these cases.

In assessing the benefits of treatment it should be realised that the maintenance of a grade of change may represent a beneficial effect, where the natural history of the disease usually operates to produce deterioration - as in the electrocardiographic changes in hypertension. Canabal (1945) estimated that 50% of electrocardiograms showing hypertrophy in hypertension are liable spontaneously to deteriorate in five years.

Emphasis must be made on one final point which emerges from a study of the correlations. Where surgical treatment has failed and the blood

pressure is uncontrolled, there is an increased incidence of continued deterioration in electrocardiograms and of progressive enlargement of the heart.

The Management of the Failures.

Ansolysen and serpasil have been used in four of the failures, (one of whom is from the temporary control group) and two are now well controlled, and one partially so. - Records of all four are detailed in the medical series.

Extension of sympathectomy from D.10 to D.4 on both sides did not succeed in controlling one of the failures, but this patient is now extremely sensitive to ansolysen and gets postural hypotension on this drug.

Bilateral adrenalectomy achieved hypotension in one failure, but replacement cortisone in adequate doses caused return of hypertension and of headaches.

Hexamethonium bromide, oral in one case and subcutaneous in the other, was able to achieve and maintain control in another two surgical failures until death claimed both these patients.

Four survivors in the failure group are complaining of symptoms and no control has been achieved, and two of the temporary control group are in a similar state.

Hypertension in Pregnancy.

In three patients complications of pregnancy dictated operation. In two of them pre-eclamptic toxaemia and in a third a diastolic pressure of 140 mms. during pregnancy caused their reference to the medical wards, regarding the wisdom of their risking further pregnancies. In all, previous pregnancies had been unsuccessful. In two of them, the operations were completed and subsequent pregnancies successful. In the third the operation was carried out during pregnancy and a live child resulted.

MEDICAL SERIES.

Methods.

Stabilisation. The initial investigations have generally occupied 4 - 7 days in hospital and, apart from those sufficiently ill to require bed rest, the patients have been unrestricted.

The blood pressure, measured four times daily, at 8 a.m., 12 midday, 4 p.m., and 8 p.m. was taken first with the patient sitting up in bed, or sitting in a chair, and then standing. The readings so obtained were charted.

After the investigations had been completed, the ansolysen and serpasil were started together. The initial dose of ansolysen was always 20 mgms. twice daily. The initial dose of serpasil was invariably .25 mgms. thrice daily. The ansolysen dose was increased by 20 mgms. twice daily, every second or third day, until satisfactory control was achieved. At the end of one week the dose of serpasil was usually advanced to .5 mgms. thrice daily.

A small number of patients appeared to respond to the initial doses of ansolysen and serpasil with prompt and considerable falls in the blood pressure. Usually ansolysen was responsible for the falls, but in a few cases the drop in blood pressure was found to be due to the

serpasil. These instances are recorded later.

Usually successive increases in the dose of ansolysen were required. In the first few days of stabilisation, the response of the blood pressure was from the chart seen to be intermittent - the blood pressure rising to its former height or higher after the effect of each individual ansolysen dose passed off, and before the next dose was due. With raising of the dose, however, this intermittent response was converted to a steady control on ansolysen twice daily, or occasionally three times daily. If the resulting chart showed levels of diastolic pressure throughout the 24 hours of 110 mms. of mercury or below, with occasional excursions to 115 or even 120 mms. during the course of several days' observations, this control was deemed satisfactory.

In only two patients in this series was satisfactory control not achieved by this means. In one, oral ansolysen to a dose of 320 mgms. twice daily failed and, in fact, a slight fall of blood pressure following each dose, was succeeded by a rise to still higher levels. In the other, violent and unpredictable falls of blood pressure followed small doses of oral ansolysen. Both these patients achieved satisfactory control on subcutaneous ansolysen.

In all other cases, satisfactory control was

achieved with oral ansolysen and serpasil and the patient was discharged, with a supply of tablets, to attend the hypertensive clinic at the out-patient department.

Out-patient Control. In the majority of patients in the series, blood pressure control on the twice daily ansolysen dosage prescribed in hospital, again became intermittent once the patient had been discharged, and the hypotensive effect of one dose could now be seen to pass off completely before the next dose was due. Considerable increase in the ansolysen dose was almost always necessary, but 24 hour-long control was not always achieved. Attempts to achieve it included increased frequency of ansolysen dose, but in effective doses, this produced side-effects of giddiness, lethargy and cramps in the legs lasting all day. This approach was abandoned. A larger dose before retiring was prescribed in some cases, but marked hypotension lasting long into the following day in several patients discouraged further trials in this direction, not least because the patients refused to repeat this experiment. With some reluctance, attempts to achieve 24 hour-long control in every ambulant patient were abandoned, and intermittent control was perforce accepted in a number of the severe hypertensives in group III

and IV and less often in group II.

Twice daily dosage with ansolysen was found to be the most satisfactory arrangement. A single dose of ansolysen provides the maximum fall in the first 2 hours and the blood pressure returns to its former level in 6 - 8 hours.

A dose of ansolysen that did not produce symptoms of postural faintness in the first one to one-and-half-hours would be unlikely therefore to have any significant effect in controlling blood pressure. The dose prescribed was regulated to produce this initial faintness. Adjustment of dose time was made to ensure recumbency for the first 1 - 2 hours after each ansolysen dose and the enhancing effect of meals on the response to ansolysen taken into account. Individual cases required individual dose schedules and shift workers a moveable scale.

Description.

The 64 patients in the medical series grouped strictly according to Keith consist of:-

	Females.	Males.	Total.
Group I	1	1	2
II	17	12	29
III	6	2	8
IV	2	4	6
	26	19	45

The remainder, comprising a total of 19 patients all showed retinal grade 2, but are excluded from Keith's group II by reason of arteriosclerotic complications of hypertension. These patients, listed as ungrouped, are recorded by sexes immediately below.

The medical series was then, as follows:-

	Females.	Males.	Total.
(From above)	26	19	45
(Ungrouped)	7	12	19
Whole Medical Series	33	31	64

Age and Diastolic Blood Pressure Levels.

The average age of the patients in each group, by sexes, with the age range in years is tabled, together with the mean diastolic blood pressure in mms. of mercury and the range.

	Females.			Diastolic B.P. in mms.Hg.	
	Age in Years.				
Group.	No.	Mean.	Range.	Mean.	Range.
I	1	51	-	108	-
II	17	48	33 - 67	136	110 - 170
III	6	42	21 - 56	141	120 - 160
IV	2	43	40 - 45	190	170 - 210
Ungrouped.	7	55	40 - 67	138	120 - 160

	Males.			Diastolic B.P. in mms. Hg.	
	Age in Years.				
Group.	No.	Mean.	Range.	Mean.	Range.
I	1	53	-	140	-
II	12	53	36 - 64	130	105 - 146
III	2	60	56 - 64	155	140 - 170
IV	4	52	43 - 62	170	150 - 200
Ungrouped.	12	53	32 - 65	139	115 - 180

It is seen from these tables that the youngest

patient in the medical series was 21 years and the oldest 67 years.

The mean ages in the males are higher than the mean ages in the females, and both are higher than the corresponding groups in the surgical series, with the exception of the females in groups III and IV, where the ages are approximately the same.

Two factors are known, which account in part, for the older average age in the medical series. Firstly, there is a greater average time lapse between reference to hospital and start of the therapy under study in the medical series: Methods of ganglionic blockade prior to ansolysen had frequently been tried in the medical patients with varying success for periods up to six years, and in four cases prior lumbo-dorsal sympathectomy had been carried out. Secondly, in the surgical series the oldest patient was 57 years of age, whereas in the medical series, 14 patients between 58 and 67 years were accepted for treatment. The influence of these factors on the different age incidence in the two series has been assessed for the females in group II, by way of example, and 3 of the 5 years difference in mean age is accounted for in this way.

It is noted in the medical as in the surgical series, that the ungrouped cases have with one

exception (the two group III males) an age incidence equal to and usually exceeding any of the patients in the Keith groups.

With regard to mean diastolic blood pressure levels, they show a continuous rise from group I - IV (the single male in group I excepted). The ungrouped cases show a mean diastolic pressure lower than the level for group III in each sex.

The above data with regard to age, do not suggest that a patient reaches grade IV after a long sojourn in one of the other groups. With regard to blood pressure levels, if these are taken to represent severity of hypertension, the authenticity of the grouping gains support; and by the same token the justification for excluding the ungrouped cases from Keith group III gains confirmation.

Symptoms and Signs in the Medical Series.

The following is a summary of the symptoms complained of, and some of the principal clinical findings. The sexes are combined.

Headache - hypertensive type	16	
other	29	
Headache - all types		45
Exertional dyspnoea		41
Dizziness		13
Tiredness		12
Chest pains, not truly anginal		9
Angina of effort		8
Ankle swelling		8
Blurring or disturbance of vision		12
Epistaxis		6
Blackouts		5
Night cramps in legs		6
Intermittent Claudication		1

The identification of a specific hypertensive type of headache is accepted, and the features have been already described.

"Blackouts" have been listed, when a momentary loss of consciousness has been reported, without suggestion or indication of a florid cerebro-vascular accident.

Ankle swelling alone, with no other evidence of congestive failure, and disappearing with rest, has not been accepted as indicating significant cardiac insufficiency.

The designation, chest pain, not truly anginal, has been applied to the complaint of praecordial oppression or tightness, usually substernal and not strictly related to effort. This symptom complained of in nine patients in the medical series, is recognised to occur in hypertension, Fishberg (1954). Effective control of blood pressure was found to relieve the symptom, and its return, unaccompanied by other symptoms, has in some patients, preceded the discovery of the return of the blood pressure to hypertensive levels. These observations suggest that this symptom is not psychoneurotic in origin (a label not infrequently applied to complaints in hypertension) but that it is related directly to the hypertension.

The symptom of angina pectoris, without clinical or electrocardiographic evidence of

myocardial damage, has not been taken to imply serious functional cardiac impairment.

In addition to the above symptoms, however, manifestations of serious functional impairment in heart, brain and kidneys, have prevented the inclusion of some of the following patients in the appropriate Keith groups.

Left Ventricular Failure - 6.

Retinal grade 2: Five patients complained of attacks of nocturnal dyspnoea. This symptom has, in two of these patients been accepted, as implying impending left ventricular failure. In the other three, attacks of cardiac asthma, crepitations in the lungs, and radiological evidence of pulmonary congestion have established its presence.

Retinal grade 4: One patient was admitted in left ventricular failure.

Coronary Thrombosis - 3.

Retinal grade 2: Recent coronary thrombosis in two.

Retinal grade 3: Recent coronary thrombosis in one.

Congestive Cardiac Failure - 11.

Retinal grade 2: Three patients had recent frank congestive cardiac failure. In three other patients with evidence of left ventricular failure (also listed above), incipient congestive failure was diagnosed, with the occurrence of peripheral oedema.

Retinal grade 3: One patient showed evidence of developing congestive failure.

Retinal grade 4: Three patients were in congestive failure, and a fourth patient with attacks of cardiac asthma showed evidence of impending congestive failure, with the appearance of peripheral oedema, (also listed under left ventricular failure).

Cerebro-vascular Accident - 14.

Retinal grade 2: In three, there was a history of subarachnoid haemorrhage (with residual impaired cerebration in one). In eight patients there was a history of cerebral thrombosis, with residual change in five (one with resulting impaired cerebration).

Retinal grade 3: One patient had a subarachnoid haemorrhage and one, a cerebral thrombosis. In neither was there evidence of residual damage.

Retinal grade 4: One case of cerebral thrombosis with no residual damage.

Impaired Renal Function.

Albuminuria: Six patients showed albuminuria in excess of a trace, with no other evidence of renal damage.

Raised Blood Urea: Renal functional impairment was found with raised blood urea in eleven patients; five patients with retinal grade 2 and six in grades 3 and 4.

Abnormal Pregnancy History.

Of the 33 females in the medical series, 3 are single, 7 married with no children and 14 women have normal pregnancy histories in altogether thirty pregnancies. 2 women had each one still-birth in a combined total of ten pregnancies. 1 woman gave a history of acute nephritis following the birth of her only child, but showed no evidence of chronic renal disease. Abnormal pregnancy history in the remaining 6 women, was classified as follows:-

Pre-existing hypertension.

4 women gave a history of the occurrence of hypertension in the early months of pregnancy.

This had been noted in eight pregnancies, all of them successfully completed with bed rest and supervision. Over and above these eight pregnancies with the presence of hypertension, two pregnancies were completely normal with total absence of hypertension.

Toxaemia of pregnancy.

2 women gave a history of eclampsia in two pregnancies and pre-eclampsia in one. Only one pregnancy out of the four was normal in respect of these women.

Radiographic evidence of Left Ventricular Hypertrophy.

In assessing the heart size, the chest films were studied and graded for evidence of left ventricular hypertrophy. The grades were none, slight, moderate and marked.

No. of patients.	No film.	None.	Slight.	Moderate.	Marked.
64	6	0	16	38	4

Electrocardiographic evidence of Left Ventricular Hypertrophy.

The tracings prior to treatment were studied, and the assessment of left ventricular hypertrophy was made, guided by the findings of Sokolow and Lyon. The gradings were none, minimal, moderate and marked.

The grades for the whole medical series were as follows:-

Left Ventricular Hypertrophy.

No. of patients.	No tracing.	None.	Minimal.	Moderate.	Marked.
64	2	1	14	23	24

Ophthalmoscopic Reports.

The cases were grouped according to the criteria of Keith on the basis of the findings on retinal examination.

Details in 61 of the 64 patients allow the following features to be tabulated.

	mild sclerosis	3
+	primary sclerosis	11
++	arteriosclerotic retinopathy	1
	attenuation	1
	attenuation and mild sclerosis	12
	attenuation, spasm and mild sclerosis	6
+++	hypertensive changes and marked sclerosis	13
	hypertensive retinopathy	8
	papilloedema	6

\+ The significance of this designation is outlined in the corresponding section in the surgical series.

++ This picture corresponds with the Foster-Moore Retinopathy, 1915.

+++ Includes one patient with papilloedema, in association with subarachnoid haemorrhage.

The distribution of these findings in the appropriate groups are as follows:-

Keith Groups.	Mld. Scl.	Prim. Scl.	A/S Rt. pthy.	Attn.	Attn. & Mild Scl.	Attn. spm. & Mild Scl.	Ht. Rt. & Mkd. Scl.	Ht. Rt. pthy.	Pda.
I	1								
II	1	7		1	9	5	6		
III								8	
IV									6
Ungrouped	1	4	1		3	1	7		

Scl. - sclerosis. Attn. - attenuation.
Ht. - hypertensive. Pda.- papilloedema.
Rt.pthy. - retinopathy.

Results in Medical Series.

Mortality.

In a 6 months - 2 year follow-up of the 64 patients in the medical series, seven patients have died, the group and percentage being as given below:-

Group III - 1 death - 13%
Group IV - 3 deaths - 50%
Ungrouped - 3 deaths - 16%

Below are tabulated the details of the patients who have died.

Deaths.

Group III - 1 death.

F.51. Survival 7 months. Admitted in congestive failure with history of angina and coronary thrombosis. Good hypotension. Died of a stroke.

Group IV - 3 deaths.

M.51. Survival 7 months. Incipient failure, little effect on blood pressure. Cause of death - uraemia.

M.43. Survival 3½ months. History of cerebro-vascular accident. Initially good effect on B.P. but therapy not closely controlled. Cause of death - sudden - unknown.

M.52. Survival 3 months. High blood urea. Good effect on blood pressure, but rising blood urea was cause of cessation of therapy. Cause of death - uraemia.

Ungrouped - 3 deaths.

F.55. Survival 9 months. Admitted with incipient congestive failure, blood urea 60 mgms.%. Little effect on blood pressure.

M.65. Survival 6 months. Admitted in congestive failure with history of coronary thrombosis and cerebro-vascular accident. Good hypotension. Died of further coronary thrombosis.

M.57. Survival 1½ years. History of angina of effort. Good hypotensive effect. Cause of death - presumed coronary thrombosis.

Effect on Prognosis.

22 patients in Keith's groups I - IV in the medical series have been followed up for 1 year or more. The number in each group, the deaths, and the percentage death rate for each group, are listed. Also listed for comparison are the figures for percentage deaths at one year, for the series without specific therapy, published by Keith and the figures for the 1 year death rate of the accompanying surgical series.

Medical Series. 22 patients - 1 year follow-up.			Keith's Series.	Present Surgical Series.
Group.	No.	% deaths at 1 yr.	% deaths at 1 yr.	% deaths at 1 yr.
I	0	-	10	0
II	13	0	12	6
III	5	20	35	9
IV	4	25	79	20

The 22 patients in the medical series, followed up for one year show in respect of prognosis an improvement in comparison with Keith's published figures. The small number of patients in the individual groups of the medical series, however, precludes any firm claims.

Comparison with the figures for 1 year death rate in the surgical series on the other hand, shows no great difference between the two series except in group III, but again the small number of cases involved permits of no significant conclusions.

The Effect of Medical Treatment on the Blood Pressure.

Before percentage estimates are given for the efficiency of medical control of blood pressure six months after discharge from hospital, certain points require clarification.

In the 64 patients initiated in therapy with ansolysen and serpasil, certain breaks in treatment occurred in the first six months.

For reasons outlined under the appropriate headings, nineteen patients discontinued part, or all, of their treatment. Three of them discontinued both ansolysen and serpasil: seven ansolysen alone: and nine serpasil alone.

In five of these nineteen patients, alternative therapy was employed and these patients have automatically been recorded as failures in control in the follow-up records.

In the remaining fourteen patients, success or failure in control of blood pressure has been recorded as and when it occurs.

These provisions will ensure a figure that represents the percentage control of blood pressure at six months for the treatment under study and provide a comparison for the results in the surgical series.

In assessing the effectiveness of medical therapy in controlling the blood pressure, initial and follow-up diastolic pressures are recorded and compared, and the responses graded into:-

Good Response. 20 mms or more fall, to 110 mms. mercury or below.
Poor Response. 20 mms. or more fall, to below 125 mms. mercury.
Failed Response. Fulfilling neither of these conditions.

The follow-up blood pressure estimation has always been made more than 2 hours (and generally 3 - 5 hours) after the preceding dose of ansolysen. The levels recorded have always been supported by similar levels at previous or subsequent visits to the out-patient department.

Effective Blood Pressure Control after 6 months.

The whole medical series has been followed up for a minimum period of six months.

Adopting the criteria outlined above, in the survey of the blood pressure responses of the 64 patients in the medical series, it was found that 37 patients, or 58%, showed good blood pressure response six months after initiation of treatment.

MEDICAL SERIES - 58% EFFECTIVE B.P. REDUCTION AT 6 MONTHS.

Pattern of Blood Pressure Control in the Medical Series.

29 patients in the medical series have blood pressure records extending over a year or more, from the initiation of treatment.

Tabulated as percentages of good, poor and failed responses and percentages of deaths, the results were as follows at three months, six months and one year.

29 Patients followed up for 1 year.

	Duration of Treatment. Months.		Years.
Blood Pressure.	3.	6.	1.
Good Response %	52	49	49
Poor Response %	27	27	17
Failed Response %	21	24	24
Deaths %	0	0	10

A slight loss of control between three and six months is suggested by these figures and in fact one patient, initially well controlled, did

show return of blood pressure to hypertensive levels in spite of careful maintenance dosage.

The figures conceal the loss of control in three patients who voluntarily discontinued treatment after being well stabilised. This is however compensated for by three other patients who were brought under control for the first time, between three and six months after the start of treatment, by increase of the dose of ansolysen.

Longer follow-up studies, at present being conducted, will reveal whether the control achieved at one year, will continue undiminished. It will be remembered that a significant number of patients, well controlled in the first six months after surgery, later relapsed.

Effect of Medical Treatment on Symptoms.

45 patients in the medical series complained of headaches before treatment.

In 26 patients they were cleared.
In 13 patients they were improved.
In 6 patients they were unchanged.

Thus improvement or relief of headaches resulted in 87% in the medical series.

MEDICAL SERIES - 87% IMPROVEMENT OR RELIEF OF HEADACHE.

This high proportion of symptomatic improvement in respect of headache has been reported elsewhere. Ashby, O'Neill and Maclean (1955) reported 85% improvement or relief of headache in

72 patients under treatment with oral pentolinium tartrate. V.Ronnov-Jessen (1955), reviewing 96 patients under treatment with oral pentolinium tartrate and some with serpasil also, reported improvement five months or later in 95% of 67 patients with headache.

Not all writers however agree that the relief of headache is a useful criterion with which to measure methods of treatment of benign hypertension. Stewart (1953) has carefully distinguished between headache following and preceding knowledge of hypertension, and from his results, he is prepared to say that nearly all headaches in benign hypertension are due to anxiety,

This has not been the impression here, for the direct association of hypertensive levels of blood pressure and headache has been already noted in the surgical series, where in relapsed cases, headaches recurred, with the patient unaware of the return of the blood pressure to hypertensive levels.

Stewart's careful studies led him to a proposal, with which experience in the present study is at variance. The explanation for the disagreement lies probably in a difference in case material. Stewart's cases gained entry to his

series purely on the basis of blood pressure levels- 120 mms. diastolic pressure was the minimum. 73% of his patients who were aware of their 'hypertension' but had no headache, showed retinal grading 1 or less, and since they were symptomless, they would not gain entrance to the present two series. However, one of the correlations he discovered seems relevant, namely that narrowing of the retinal arteries was more common in his patients with headache, than in those without it. Keith's criteria for retinal grading outlines this fact.

Exertional Dyspnoea.

41 patients in the medical series complained before treatment of shortness of breath on exertion, ranging from the mildest exertional dyspnoea, to orthopnoea, in the presence of congestive cardiac failure.

Results of treatment are as follows:-

21 patients showed improved exercise tolerance at follow-up - 51%.
17 showed no change - 41%.
3 found increased impairment - 7%.

MEDICAL SERIES - 51% IMPROVEMENT IN DYSPNOEA.

It must be stated at this point that of the twenty-one patients whose exercise tolerance improved with treatment, seven were in fact admitted to hospital in incipient or frank

congestive failure. In these seven patients, in addition to ansolysen and serpasil, digitalis and mercurial diuretics were employed for the relief of congestive failure and improvement in exercise tolerance must be associated in large measure with the latter two drugs. A faithful assessment of the effects of the medical treatment under study - ansolysen and serpasil - will preclude the recording of benefits when other drugs are involved. These seven cases are therefore excluded to give:-

14 patients (34%) with improvement in dyspnoea.

This figure may be compared with the surgical series, where no patient was in failure at operation. It should be remembered however that ansolysen itself may specifically relieve pulmonary congestion.

Congestive Cardiac Failure.

Altogether eleven patients were in incipient or frank congestive failure and with conventional methods, mercurial diuretics and digitalis in addition to ansolysen and serpasil, nine were relieved of signs of failure. Further, seven of these experienced improved exercise tolerance.

Two patients continued to show evidence of failure.

Electrocardiographic Changes after Treatment.

Reversal of the electrocardiographic changes interpreted as hypertrophy were noted in follow-up tracings. The improvement was listed as 'marked', if a study of all leads allowed upgrading of the tracing on the pre-treatment record. A definite improvement but not justifying regrading was listed as 'slight'.

Follow-up tracings were available in 56 patients in the medical series, with results as follows:-

Initial hypertrophy was deduced in 55.

12 showed slight improvement.
12 showed marked improvement.

Thus improvement was noted in 24 or 44%.

No change was noted in 19 - 34%.
The records were worse in 12 - 22%.

MEDICAL SERIES - 44% IMPROVEMENT IN ELECTROCARDIOGRAPHS.

The electrocardiographic improvement when marked took some months to establish itself - in one patient whose records are in the appendix (Plate IVa) improvement continued over a whole year, without change of treatment, and without apparent alteration in the well controlled blood pressure.

As emphasised in the surgical series, it must be remembered in the assessment of the electrocardiographic results, that the tendency

in the natural history of hypertension is for the electrocardiographic picture of hypertrophy to deteriorate. No change may therefore represent an achievement.

Doyle (1953), reported improvement in 76% of electrocardiograms after three to thirty months' treatment by methonium compounds. The route for administration of the drug was subcutaneous in the majority of his patients, and he recorded no failures in blood pressure control. The present series does carry a failure rate in blood pressure control, and this fact may explain the smaller percentage of improvements in electrocardiograms in this series, as compared with Doyle's series.

Chest X-Rays after Treatment.

Follow-up six foot chest films were available in 39 patients in whom initial hypertrophy had been recorded. The results are as follows:-

No change was noted in 24.
The heart was larger in 8.
(Initial congestive failure was present in 2 of the patients).
The heart was smaller in 7.

That is, in 18% there was evidence of reduction in heart size.

MEDICAL SERIES - 18% REDUCTION IN HEART SIZE.

In one of these patients the reduction in heart size may have been associated with clearing

of congestive failure by mercurial diuretics. In the others, no such explanation is possible.

The validity of results based on the assessment of alteration in heart size by comparison of postero-anterior six-foot chest films is often questioned. Close correlation of the results obtained in this way with the other clinical findings appeared however to confirm the value of the method, and when correlation fails, the disagreement is usually found to be significant.

For example, the discovery of cases in whom the heart shadow was reported to be larger in spite of apparently successful treatment, has focussed attention on the role of serpasil in fluid retention.

Ophthalmoscopic Follow-up Medical Series.

Follow-up examinations were available in 24 and showed:-

Attenuation with mild sclerosis in 7 - attenuation less in 1, no change in 5, appearance of spasm in 1, more sclerosis in 1.
Mild sclerosis in 1 - no change.
Attenuation, spasm and mild sclerosis in 3 - attenuation less in 1, spasm still present in 2.
Hypertensive retina with marked sclerosis in 2 - no change in 1, developed atrophic disc in 1.
Hypertensive retinopathy in 7 - cleared in 6, unchanged in 1.
Papilloedema in 4 - cleared in 3.

To summarise - 23 patients exhibited potentially reversible changes in the retina and

improvement occurred in 11 - 48%.

MEDICAL SERIES - 48% OPHTHALMOSCOPIC IMPROVEMENT.

Maintenance of Medical Therapy and Complications.

Dose of Ansolysen.

The average total daily maintenance dose of ansolysen, 3 months or more after discharge from hospital, was calculated for the patients in each group:-

Group I	40 mgms.	Group III	273 mgms.
Group II	175 mgms.	Group IV	287 mgms.
	Ungrouped 174 mgms.		

The average dose required to maintain control of blood pressure is thus seen to rise from group I to group IV. It will be noted however, that the doses required to maintain control in groups III and IV are similar as are those in the ungrouped patients and group II cases.

The highest daily dose employed is 480 mgms. (160 mgms. x 3) - two patients are at this dose level - one in group IV and one ungrouped. In some patients whose blood pressure was still uncontrolled, dosages of this magnitude or higher were precluded by the severity of side effects.

Minimal Doses of Ansolysen.

It will be apparent from the average maintenance dose levels just recorded, that in the majority of patients, considerable increase of the initial dosage of ansolysen was required to achieve and

maintain control of blood pressure.

In a number of patients in the medical series, however, the initial doses of ansolysen, which were prescribed, remained unaltered. Altogether fourteen patients were maintained on total doses of ansolysen of 80 mgms. or less in the day, by reason of adequate control at this level, or intolerance of higher doses, and details of these patients are of interest.

In three patients, serpasil is considered to be the actual hypotensive agent, because of the sudden falls in blood pressure following its addition to the treatment. In one of them the role of serpasil seems to be established because when this patient voluntarily discontinued both ansolysen and serpasil, and the blood pressure relapsed, it was brought under control once more by the use of serpasil, prescribed alone.

One patient, a male, with an initial blood pressure of 190/140, weighed 16 stones. He was persuaded to lose 4 stones and the blood pressure is now constantly in the region of 170/95.

Three patients, with no unusual clinical features, are apparently well controlled on these small doses of ansolysen, and on serpasil.

In two other patients, even these small doses of ansolysen produced side effects and both discontinued the pills; one has relapsed and the other appears to be in remission.

Two patients, previously subjected to lumbo-dorsal sympathectomy were intolerant of higher doses.

Finally, in three patients, consisting of two with recent cerebro-vascular accidents and one with recent angina, small doses of ansolysen continued to produce marked falls in blood pressure.

Once it was appreciated that in the majority of patients, the average daily maintenance dose of ansolysen was far in excess of the initial dose, the exceptions, detailed above, appeared to require explanation.

From a study of these exceptions the impression was gained that apparent control on minimal doses of ansolysen implied either that:-

(1) the ansolysen was superfluous,
    (a) because some other drug (serpasil) was the sole effective agent, or
    (b) because the need for any treatment had disappeared, as a result of remission of the hypertension;

or that:-

(2) the patient was unduly sensitive to ansolysen because of special circumstances and these were:-
    (a) after lumbo-dorsal sympathectomy;
    (b) in the presence of arterio-sclerosis - particularly after cerebro-vascular accident with impaired cerebration;
    for completeness may be added
    (c) in hypertensive encephalopathy, though no cases appear in the present series.

Side Effects of Ansolysen.

Hypotension:- The symptoms associated with hypotension following oral ansolysen, were dealt with by alteration of dose schedules, as explained in the section on methods. These symptoms include postural dizziness, occasional fainting, sometimes aching in the back or legs, and occasionally in the arms. In the majority of patients these effects are readily circumvented.

Special circumstances however make hypotension following ansolysen disabling, and at times dangerous. As outlined in the previous section, the presence of generalised arteriosclerosis was found by experience to impose caution in dose regulation, and instances were provided where small doses of ansolysen were often found to be adequate in these circumstances.

Confirmatory evidence of the potential danger of ansolysen in the presence of cerebral arteriosclerosis is provided by details of the six additional cases set out below:-

One patient with a recent subarachnoid haemorrhage responded with violent and unpredictable falls in blood pressure, to the smallest doses of oral ansolysen and was transferred to subcutaneous ansolysen.

One patient with a history of angina pectoris had the early doses of ansolysen discontinued following a cerebral thrombosis.

In four patients, each with a history of cerebro-vascular accident, the reduction of average ansolysen doses was required: in two of then to avoid tingling following each dose in previously hemiplegic limbs: and in two of them, to avoid attacks of unconsciousness which either directly followed, or increased in frequency after, a rise in the dose of ansolysen.

A further category of patients (none in this series) appears to demand cautious employment of oral ansolysen - those patients admitted with hypertensive encephalopathy. Extreme sensitivity is apparent, and a violent and prolonged fall in blood pressure often follows one dose of 20 or even 10 mgms. of oral ansolysen. Another

circumstances which may enhance the hypotensive effect of ansolysen is suggested by the following details of a patient in the medical series.

One patient in group IV, with raised blood urea, developed prolonged hypotension with coma. It is surmised that impaired excretion led to cumulation of ansolysen. The injection of methedrine caused a violent return to hypertensive levels. This return is almost certainly associated with sensitisation of blockaded ganglia to pressor agents (a state which is demonstrable experimentally).

It was noted in the previous section that lumbo-dorsal sympathectomy appears to sensitise the patient to the hypotensive effect of ansolysen. One of the two patients instanced, developed severe postural hypotension on all but the smallest doses of ansolysen. It should be mentioned that two other similar cases withstood average doses of ansolysen.

Finally two patients without complications, appeared to be satisfactorily stabilised in hospital on average doses of ansolysen, but this was discontinued because of severe dizzy attacks, after return home.

Lethargy. Twelve patients complained of a general lethargy associated with the ansolysen. Eight of these patients preferred the lack of energy and tiredness to their previous headaches or exertional dyspnoea, but felt their efficiency was, none the less, impaired. Three were persuaded to continue with ansolysen in view of objective evidence of

benefit in electrocardiograms and blood pressure levels. One patient discontinued the ansolysen because of the extreme tiredness it caused, but her headaches have returned with relapse of blood pressure.

Constipation. This has been troublesome in a few cases, and regular aperients have been found necessary. In one patient prostigmine injections are required once weekly to maintain bowel function. This patient apart, no serious bowel upset has occurred, and paralytic ileus has not been seen.

Dry Mouth. A few patients have complained of dry mouth, helped by boiled sweets. One patient, not in this series, found prostigmine tablets 15 mgms. two or three times daily, to be of great value.

Loss of Accommodation. This symptom, initially troublesome, has been found to lessen with time, but in three patients special lenses have been necessary and are satisfactory.

Acute Sensitivity Reaction. One patient developed joint swelling following the initial dose of ansolysen and the latter was discontinued.

Altogether, in eleven patients, the oral ansolysen was discontinued. Severe hypotension,

lethargy and acute sensitivity reaction are seen to account for six of these instances. The other five are accounted for by discontinuance in a group IV patient in the face of a rising blood urea: in three patients because of failure of control despite high dosage: and by one patient who discontinued her pills on admission to another hospital for minor surgery.

Effects of Serpasil.

Depression. On discharge the serpasil dose was usually .5 mgms. t.d.s. In eight patients the serpasil was discontinued with the onset of severe depression, and one of them required admission to a mental hospital. The depression was usually associated with agitation and in two patients tremor and Parkinsonian features were manifested.

The eight patients comprise:-

Essential hypertension - uncomplicated 2.
with asthma 1.
with subarachnoid 3, one with impaired cerebration.
with cerebral thrombosis 2, both with impaired cerebration.

The side effect of depression has appeared to be more readily produced when the dose was maintained at .5 mgm. t.d.s. All the patients still having serpasil are now maintained on .25 mgm. twice or three times daily. No attempt was made to

replace serpasil with another rauwolfia alkaloid, though Smirk and McQueen (1955) provided evidence that rescinnamine was less liable to produce mental depression than was reserpine.

In three patients the serpasil was discontinued at the same time as the ansolysen, when control was seen to have failed.

In one patient, the serpasil was discontinued by the family doctor to avoid the possibility of depression.

Altogether twelve patients discontinued serpasil.

Exertional Dyspnoea. Four patients complained, while on treatment, of increased dyspnoea on exertion, the cause of which was suspected to be serpasil. In one patient, an attempt was made to establish serpasil as the cause, but the attempt was inconclusive:-

> This patient was in incipient congestive failure. The serpasil was discontinued for one month and the patient, who claimed to feel less breathless, required neptal injections less frequently than when she was having serpasil as well. The serpasil was re-started and she, when seen one month later, claimed to feel breathless once more. Certainly the heart size on X-ray had increased, but weight charts were inconclusive.

The effect of serpasil on the symptom of dyspnoea on exertion was investigated by McGregor and Segel (1955). They found that 6 of 19 patients first manifested congestive failure while

on serpasil, and they suggested that fluid retention may be the precipitating factor in patients in whom failure is a possibility.

Nasal Stuffiness. The assessment of exertional dyspnoea in patients on serpasil was sometimes difficult by reason of this side effect of nasal stuffiness, which may cause difficult breathing, mistaken by the patient for exertional dyspnoea. Nasal stuffiness was complained of, in over one-third of the patients and reduction of dose gave some relief. Antihistamine nasal drops were of considerable help.

Effect of Serpasil on Blood Pressure. Three patients responded specifically to serpasil and the ansolysen was stopped in two of them without loss of control. The third patient, with a past history of angina pectoris, experienced anginal symptoms when the serpasil and ansolysen were given together, but not when they were spaced.

In several other patients in the medical series, it was suspected that serpasil was the main hypotensive agent. Though the small number of cases under observation in this series permits no more than an impression, those patients in whom serpasil appears to have a specific hypotensive action immediately, seem to have some distinguishing features. They appear to belong to a group in which primary sclerosis is mentioned by the

ophthalmologist. They are often plethoric, and they may have palpable radial arteries. Further, the hypertension is labile and, in combined therapy, the ansolysen dose does not need re-adjustment after discharge from hospital.

Medical Therapy in the presence of Impaired Renal Function.

In the medical series thirteen patients had impaired renal function. - Details are given below:-

In 1 the blood urea was normal,
in 2 between 40 and 60 mgms.%, and
in 10 over 60 mgms.%.

4 were in group IV;
4 were in group III;
5 occurred in the ungrouped patients.

Blood urea estimations were made on these patients during therapy and in one patient in group IV, a rising blood urea caused the ansolysen to be stopped. In all the others the blood urea remained high. Two have since died from presumed cerebro-vascular accidents. With the exception of the patient already mentioned, the treatment did not appear to affect the level of blood urea.

The Successes and Failures in the Medical Series.

A study of the medical series at six months allows us to classify the patients with reference to blood pressure control into successes, partial successes and failures. The criteria of

successful, partial and failed responses have already been outlined. In only one instance in the medical series, has a successfully controlled patient relapsed while still on treatment, so that the term temporary success is hardly applicable.

Successful control has been achieved in 37 patients.
Partial control has been achieved in 14 patients.
And failures in 13 patients.

The distribution of these categories of blood pressure control in Keith's groups is now tabulated.

	I	II	Ungrpd.	III	IV	
No. of patients in groups.	2	29	19	8	6	
Successes	2	19	11	5	0	
Partial successes.	-	6	5	1	2	
Failures.	-	4	2	2	2	(+ 2 deaths).

Thus the successes comprise, 66% of the patients in group II, 57% of the ungrouped patients and 62% of the patients in group III.
100% success is achieved in group I and none in group IV.

Certain correlations of these reults in respect of blood pressure control are now made with the alteration in symptoms and clinical features.

1. Headache.	Complete Relief.	No Relief.
Successes	76%	4%
Partial Successes	20%	10%
Failures	50%	40%

2. Exertional Dyspnoea.	Improved.	Worse.
Successes	58%	8%
Partial Successes	44%	-
Failures	33%	17%

3. Electrocardiograms. +	Improved.	Worse.
Successes	55%	16%
Partial Successes	23%	23%
Failures	36%	36%

4. X-Rays.	Heart Size.	
+	Smaller.	Larger.
Successes	16%	20%
Partial Successes	33%	17%
Failures	13%	25%

5. Fundi. +	Better.	Worse.
Successes	46%	8%
Partial Successes	50%	-
Failures	29%	-

* Signifies % improvement in potentially reversible grades.

These correlations show some noteworthy findings.

In general they confirm the benfit of blood pressure reduction as applied to headache, exertional dyspnoea, electrocardiographic changes and ophthalmoscopic appearance. It is to be noted that with regard to these four features, worsening of the grade occurs in only a small percentage of cases.

By contrast in the failed control cases, 40% of headaches were unrelieved, exertional

dyspnoea increased in 17%, electrocardiograms deteriorated in 36% and X-rays became larger in 25%.

However it is noted that in medical treatment as in surgical treatment, improvements are not restricted to the well controlled patients.

The increase in size of heart shadow in 20% of the records available in the successes, is surprising and is not understood. It is possible that serpasil may have produced fluid retention in some of these patients. Three of them showed signs of incipient failure prior to treatment, and might therefore be vulnerable if serpasil has the effect of producing fluid retention (McGregor and Segel, 1955).

Management of Failures.

Two patients required ansolysen injections, in one because the blood pressure could not be controlled in hospital with 640 mgms. of orally administered ansolysen daily. The other had had a cerebro-vascular accident and the response to oral ansolysen was unpredictable.

Mecamylamine has been started in three of the failures, and the side effects in higher dosage of ansolysen, necessary to maintain even partial control, have been reduced by its use.

Apresoline in two cases has been added to ansolysen and control of blood pressure improved, but tachycardia limits the dose employed.

COMPARATIVE TABLES.

MEDICAL SERIES.

OBJECTIVE.	SUBJECTIVE
48% OPHTHALMOSCOPIC IMPROVEMENT.	87% RELIEF OF HEADACHES.
44% E.C.G. IMPROVEMENT.	51% RELIEF OF DYSPNOEA.
18% REDUCTION IN HEART SIZE.	
58% SIGNIFICANT REDUCTION OF BLOOD PRESSURE AT 6 MONTHS.	

SURGICAL SERIES.

OBJECTIVE.	SUBJECTIVE
64% OPHTHALMOSCOPIC IMPROVEMENT.	81% RELIEF OF HEADACHES.
50% E.C.G. IMPROVEMENT.	33% RELIEF OF DYSPNOEA.
46% REDUCTION OF HEART SIZE.	
50% SIGNIFICANT REDUCTION OF BLOOD PRESSURE AT 6 MONTHS.	

E.C.G's. & X-RAYS. Percentage given is improvement in available records showing hypertrophy in follow-up records available.

FUNDI. Percentage given is improvement of potentially reversible changes in follow-up records available.

DISCUSSION.

The results in a medical and surgical approach to the problem of hypertension have been presented. The present study was undertaken with the object of gauging the success of a current treatment of hypertension (oral ansolysen and serpasil) by means of comparison with a standard. The standard is the surgical series, a carefully investigated and recorded series, in which the first patient was operated on ten years ago. This surgical series forms a ready made control, and we may draw some conclusions and provide an interim report on whether the medical treatment is achieving, and is likely to continue to achieve, the results which followed surgery.

The results of treatment in the two series are now compared in detail; a summary is provided in table form on page 116.

The blood pressure responses to treatment must first be examined, but preliminary consideration of the blood pressure records, from which these responses were calculated, is relevant.

The initial blood pressure reading was obtained, as described in the introduction, at the first formal examination after admission, and the value of this reading is often questioned. The emotional upset associated with admission to

hospital is said to provide unduly high values in blood pressure readings in the first 24 hours. While it is true that rest in bed for a few days will usually furnish readings below the initial value, return of the patient to unrestricted activity will nearly always be accompanied by a return of the blood pressure to the previous high levels.

I believe that the value recorded as the initial blood pressure does, in fact, represent the pre-treatment blood pressure level in the ambulant patient, and this is the level that treatment seeks to alter. Apart from the important consideration, that it was always available, taken under fairly comparable conditions, the initial reading had these recommendations:- It was usually below, and certainly never exceeded, the level obtained in the out-patient department, when the patient was first referred (the consultation blood pressure), and the initial value had the support of casual blood pressure readings taken in the out-patient department prior to admission, in the many cases in whom a period of out-patient observation preceded treatment.

The follow-up readings in the medical series were always made 3 hours or more after the previous dose of ansolysen. This procedure prevented the

recording (in the standing blood pressure readings) of the immediate postural hypotension that almost invariably follows an adequate dose of ansolysen, for it is conceded with Blainey (1952), that immediate postural hypotension is no indication of good control. This consideration apart, recumbency in the first hour or two was practically always necessary, if the ansolysen dose was adequate for prolonged control.

If, however, postural hypotension was recorded 3 hours after the previous dose of ansolysen, then the levels obtained in this way were accepted as indicating good control, provided they fulfilled the necessary criteria. To omit to accept them, would be to deny control in patients, in whom the other clinical findings proclaim success.

Three final points are emphasised with regard to blood pressure records. Firstly, a fall of 20 mms. in the diastolic pressure was accepted as significant, because random variations seemed to be rarely of this magnitude. Whitelaw and Smithwick (1948) considered such a fall to be significant though Platt (1950) demurs. Secondly, the consistency of out-patient blood pressure readings by different observers, over quite long periods, was striking and confirms my belief that casual

blood pressure readings are valuable. Finally, the close correlation of improvement in clinical findings, with the control of blood pressure as recorded by the methods outlined, appears to support the validity of the methods.

In the first six months, the actual results in blood pressure control are seen to favour the medical as compared with the surgical series 58% : 50%. From the records available, we may study, in the surgical series, the pattern of control over a period of years; in a five-year follow-up of 49 patients, success in controlling the blood pressure was achieved in 53% at six months, 47% at one year, 26% at four years and 26% at five years; in 18 patients followed for eight years after operation, 28% had maintained good control.

These figures show a loss in control which increases with the time since operation, but they must be viewed with these observations in mind:- There appears to be a considerable proportion of permanent successes after sympathectomy; and relapse, in a clinically recognisable fashion, occurs in a significant number of patients 2 - 3 years after operation, after which period, relapse is rare.

A satisfactory explanation has not been

found for these relapses, but they are associated in some way with the type of operation. In the patients subjected to lumbo-dorsal sympathectomy there were 33% relapses whereas, in the extended lumbo-dorsal sympathectomies, the figure was 12%. It was of interest to find that 3 of the 4 upper lumbar and splanchnic sympathectomies achieved initial success, though one of these relapsed.

The best results in surgery were obtained in groups I and II. 66% of group II cases were well controlled for six months and 34% permanently controlled.

These results closely resemble those recorded by Palmer (1947) and quoted on page 74, where it will be seen that relapse is not restricted to this series.

It will be noted that there is a considerable proportion of cases, mostly in groups III and IV, in which operation is a complete failure.

The medical series, with 58% of patients controlled at six months, improves on the surgical series. In a group of 29 patients followed for one year, the percentages controlled at three, six and twelve months were 52%, 49% and 49% respectively. There appears to be no reason to expect relapse on medical treatment, but there are important reservations. Medical 'sympathectomy' requires constant attendance and careful

out-patient control; side effects exist and serpasil depression may be dangerous; further some patients refuse to continue treatment. Fortunately symptomatic benefit in the well controlled cases encourages most patients to persevere.

Cases in groups I, II and III can apparently be controlled with the appropriate doses of ansolysen, but though symptomatic and objective benefit is achieved in group IV cases, the blood pressure is rarely controlled with oral ansolysen and serpasil.

Symptomatic benefit in the relief or improvement of headache occurs in a large percentage of the patients so affected in both series, 87% : 81% in favour of medical treatment. Experience in the present study supports the view that the relief of headache is a valuable indication of success in treatment of hypertension, and this applies even when the blood pressure is uncontrolled.

In the relief or improvement of dyspnoea on exertion, medical treatment scores 51% as compared with 33% for the surgical series. It must be remembered however, that a number of patients in the medical series, in incipient or frank congestive failure had the benefit of digitalis and mercurial diuretics in addition to ansolysen

and serpasil, and relief of congestion by these additional remedies may have increased the percentage of improvement in the medical series. It should also be noted in passing, that some patients in the medical series appeared to experience increased dyspnoea on exertion while on treatment, and serpasil was suspected as the cause.

Improvements in electrocardiograms were noted in 44% of potentially reversible tracings in the medical series, and in 50% in the surgical series. In both series the close correlation of improvements in electrocardiograms with control of blood pressure and perhaps more significant, the higher proportion of deteriorations in the failures, emphasises both the value of controlling the blood pressure and the value of electrocardiography as a method of checking that control. Improvements in electrocardiograms do however occur in the absence of evidence of control of blood pressure. It is of interest to record that some electrocardiographic tracings have maintained for eight years, the improvements which followed operation.

There is a large discrepancy in the results, in the two series, of the radiological evidence of reduction in heart size. In the surgical

series 46% of comparable films initially showing hypertrophy showed reduction: in the medical series only 18%. Radiological evidence of alteration in heart size is often closely questioned, but the radiological reports appeared usually to agree with the other clinical findings and when they did not, the X-ray evidence withstood close scrutiny. I think the explanation for the discrepancy in the results of the medical and of the surgical series must be looked for, outside the method and the following facts seem relevant. 24-hour-long control of the blood pressure in the successful surgical cases may more efficiently lighten the load of a hypertrophied, dilated heart. There is in the medical series a factor, serpasil, which may, by fluid retention either cause enlargement, or prevent reduction in size of the heart.

> The report of a larger heart when the blood pressure was controlled, when the patient had lost her headaches and when the E.C.G. had not deteriorated was striking. This happened in more than one instance in the medical series, and the patient who usually claimed to feel better, was, nevertheless, more short of breath on treatment.

A final factor may have had a bearing on the results. The writer who personally assessed the initial grades of hypertrophy in the medical series may have applied an interpretation wide enough to include hearts

incapable of reduction in size, i.e. normal. A relative reduction in the percentage of successes in the medical series would inevitably follow. It should be stressed that the writer did not make the comparisons of films before and after treatment, and the significant finding, in the medical series, that as many hearts became enlarged in the successes as in the failures cannot be accounted for by differences of interpretation.

The ophthalmoscopic reports favour the surgical series 64% : 48% in respect of improvements in potentially reversible changes. The term spasm figures less often in the medical series than in the surgical series. It may be that the longer period of selection for the surgical series, from before 1946, until 1952 has led to the accumulation of a greater number of patients showing retinal spasm in the surgical series. Certainly those patients in whom spasm was reported in the retina, appeared to provide a large proportion of the surgical successes, and the disappearance of spasm after operation adds to the percentage of improvements. The improvements in retinae do not correlate well, with control in blood pressure. This is a general experience. Platt and Stanbury (1950) report clearing of papilloedema in many cases in their series in the absence of blood pressure control.

The detailed examination just conducted of the results in the two series leads, I believe, to the following conclusion. Medical treatment, as applied here, has paralleled the results of surgical treatment, in respect of the subjective and objective benefits studied and in respect of blood pressure control. Furthermore if relapse is avoided in the medical series, medical treatment may be expected to improve on the results of surgery in these aspects.

The most valid method of assessing a treatment of hypertension is, however, the effect on prognosis. In view of the short follow-up available in the medical series, direct prognostic evaluation is not possible. Nor do I believe that it will ever be possible, with a current treatment of hypertension. To allow of valid prognostic comparisons, it would require both the maintenance of a series of patients on one therapy for five years and the running of an untreated control series. The first requirement is impractical if not unjustified, certainly the second is unethical.

The present investigation is a serious attempt to circumvent these difficulties. The effect of the surgical series on prognosis was established by comparison with series published in the literature.

Since the medical series is seen to closely parallel the surgical series in respect of blood pressure control and subjective and objective benefits of treatment, we may reasonably infer that medical treatment will have a like influence on prognosis, and in the absence of relapses may better the surgical prognosis.

What effect did surgical treatment have on prognosis? The claim for improvement in prognosis was put forward, particularly in group II - the mortality rate at five years was 16% compared with the expected 46%. I have calculated the net gain at five years for the surgical series under review and out of 64 patients, 12 survived above expectation.

Most reports of surgical treatment claim improvement in prognosis, but there is a considerable weight of authoritative opinion against the justification for such a claim.

One difficulty appears to be that Keith's prognostic studies are not granted unqualified acceptance. Later classifications of hypertension have appeared, in which Keith's concept of an active hypertensive process is lost and in which arteriosclerotic complications of hypertension are afforded prognostic significance. The reasons for adopting Keith's grouping have been fully

discussed already, but during the study these further points emerged:- the dose of ansolysen required for control rose from group I to group IV, and if this dose is any indication of the severity of the hypertension, then group III and IV are closely allied: in those patients who are excluded from Keith's groups, by reason of arterio-sclerotic complications of hypertension, the average age is higher, the average blood pressure lower, and the ansolysen dose smaller, than are to be found in group III (Keith). Justification for excluding these cases from group III (Keith) is therefore established.

Keith's prognostic conclusions seem unassailable, and the claim is confidently made, that the prognosis in the surgical series does in fact improve on the natural history of the disease.

When the results of surgery are appreciated, it is difficult to understand why surgical treatment, even before methonium therapy was fully established, should have been largely abandoned.

This particularly so, when no efficient alternative treatment was immediately available. It may have been that successes were deemed too few to justify major surgery with its attendant mortality and unpleasant side effects, and the inability to predict success was certainly a great disadvantage.

I believe that the results recorded in this study justified these operations. With regard to the other objections, the operative mortality in the present series was less than 2%, and as for side effects, the majority of the patients appeared to regard the discomfort a small price to pay for the relief of their headaches. Further, although it was not possible before, success may be predicted because hypotensive agents themselves provide now a possible screening test. This is illustrated by the following case record from the surgical series.

F.32. Initial B.P.220/150 - severe headaches, occipital and vertical on waking for 6 months. Diastolic pressure varying in ward between 120 - 140 with occasional falls to 110. She was stabilised on hexamethonium bromide injections, 100 mgms. three times daily. Severe postural faintness after each injection caused the dose to be gradually reduced to a dose of 25 mgms. three times daily at the end of 3 months. The injections were stopped and her headaches returned. The B.P. was 220/120. She was offered surgery in place of the injections, agreed and now 4 years after the operation the blood pressure levels are consistently 150/90 and she is well satisfied.

There was, it should be mentioned, one exception in this inability to predict success. Patients with peptic ulceration are liable to respond with extreme hypotension to section of sympathetic pathways; 4 of 6 patients with ulcer dyspepsia or history of haematemesis achieved

hypotensive levels after operation.

At all events, sympathectomy for hypertension was abandoned.

With the advent of the methonium drugs, and with the realisation of the irregular and unpredictable absorption from the bowel of the earlier members of the group, parenteral therapy was preferred. Reluctance to impose either by injection or by oral dosage, an exhausting regime, caused the use of these drugs to be restricted to cases in whom treatment was imperative and in whom benefit could be proved. Group IV cases fulfilled these criteria, for improved prognosis in such a rapidly fatal state could readily be established. This restriction of the indications for treatment is revealed by the following quotation. "Because of the somewhat burdensome nature of the regimen we decided to limit its use to young and middle-aged benign hypertensives whose illness was complicated by left heart failure, retinitis or transient encephalopathic attacks, or malignant and pre-malignant hypertension". McMichael,(1955) A limitation in the indications for treatment seems also to be imposed by the concept of high blood pressure as a graded characteristic, laying emphasis on the height of the blood pressure levels and drawing away from

Keith's concept of an active hypertensive process which may be staged in its severity.

Pickering (1956) places the following indication for treatment sixth in a list which is headed by malignant hypertension, "a diastolic pressure persistently of 140 or over in a patient aged 40 years or more, or a diastolic pressure persistently of 130 or over in a patient aged less than 40; the discovery of an effective treatment with a low nuisance value will reduce these limits".

A plea is made that in hypertension other than the malignant phase, a carefully controlled experiment is required to assess properly, the justification for therapy, apart from those cases where treatment is obviously urgent.

These views exclude from use of ganglion blockade a large number of hypertensives and the problem of their treatment is I believe the subject of Platt's enquiries (1956). Platt states that he leaves his mild cases of hypertension untreated, but the malignant cases deserve urgent methods and ansolysen is given. The intermediate cases, however, of severe hypertension, in which the diastolic blood pressure was not less than 120 mmg. of mercury when taken on several occasions, usually during an initial period of rest in hospital, were the subjects of a trial of reserpine. Reference

has already been made to the depression caused by serpasil, and the danger of this complication makes me believe that its use should be restricted to those cases in which it is of proved benefit and that it should not be used in combined therapy.

It is a generally accepted fact that there is a group of cases considered not sufficiently benign to leave alone, but not ill enough to justify heroic remedies. It must be agreed that injection therapy would not be justified, but these by inference are group II cases, and from the results in the present series I believe we have a therapy for these patients which is not too rigorous to allow of prolonged out-patient treatment. I believe that in the past, they would have been treated by lumbo-dorsal sympathectomy with results though unpredictable, nevertheless excellent symptomatically, and with improved prognosis. With advance in treatment and the severe restrictions imposed by insistence on rigorous methods of ganglionic blockade, this group has been excluded from these treatments. It is felt they are not severe enough to justify such an approach. This group however merits close attention, for here can be derived the greatest benefits of treatment, and a revaluation of the results of lumbo-dorsal sympathectomy in this group will set the target.

If we accept the view that malignant hypertension is a complication of such cases it would be wrong to await the development of malignant hypertension when a therapy is now available.

The medical series justifies the belief that oral ansolysen, possibly combined with serpasil, is of proved benefit. When malignant hypertension is present however, in the few cases in this series, symptomatic relief and clearing of eye grounds have been achieved, but control of blood pressure is disappointing. This may best be achieved by injection.

CONCLUSIONS.

1. Lumbo-dorsal sympathectomy is a valuable therapy in essential hypertension, improving the prognosis on the natural history of the disease, providing symptomatic relief in the large majority, producing reversal of retinal and electrocardiographic changes and effecting reduction in heart size in a significant proportion. The best results are in group II, Keith.

2. Oral ansolysen and serpasil followed from 6 months to 2 years, as far as the follow-up goes, achieve all that surgery does.

3. The efficiency in medical control of blood pressure is impaired by the need for constant

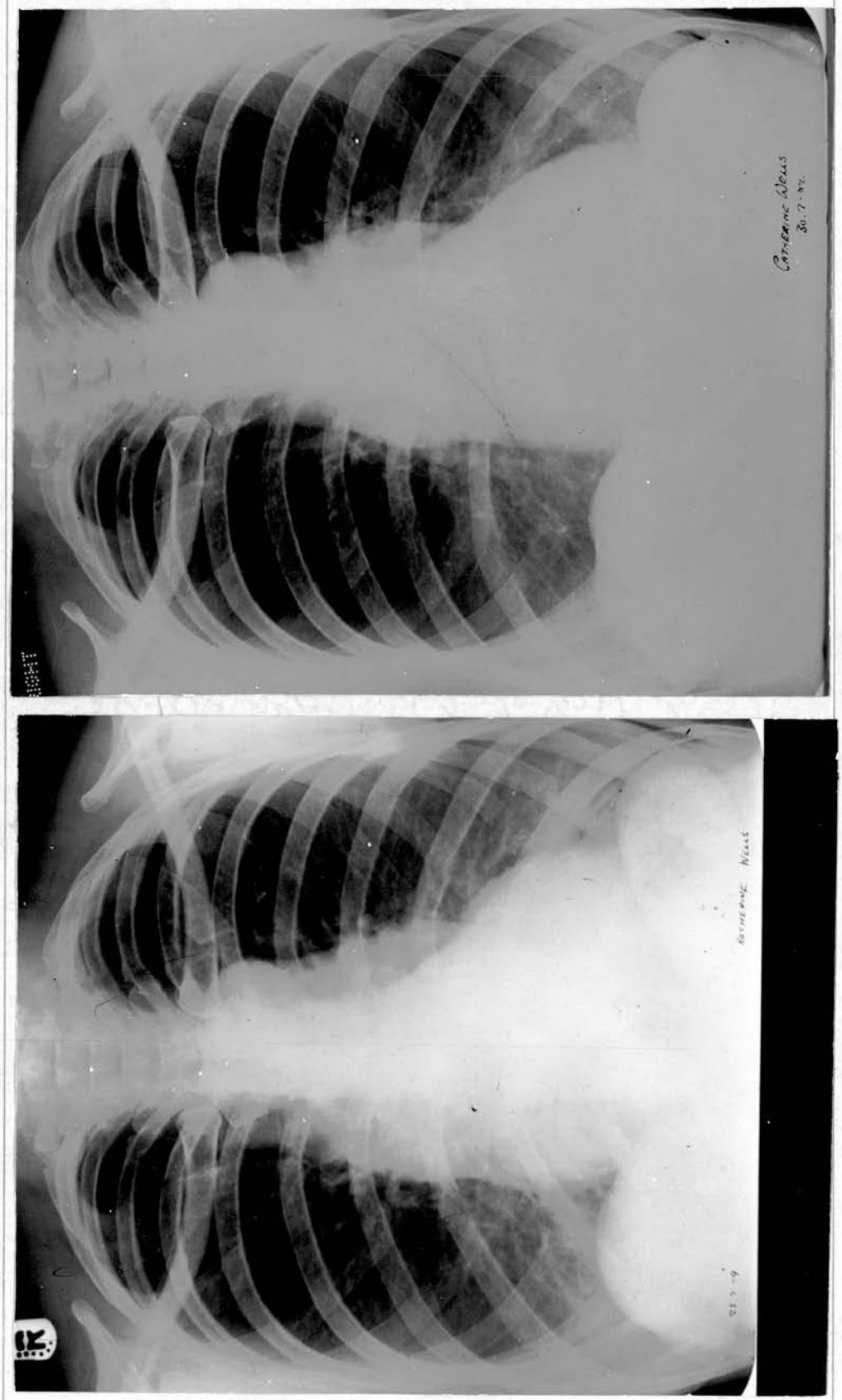
attendance and close supervision and in selected cases responding to medical therapy, surgery might now be contemplated with a reasonable assurance of success.

4. The side effects of serpasil are sufficiently frequent to suggest that it should be used alone in patients who are found to respond to it alone, and that it should not be used in combined therapy.

5. A group of cases of essential hypertension, group II Keith, which provided the best results of surgery are in danger of being denied specific therapy for with some current methods of treatment the discomfort of treatment may exceed that of the condition.

6. If it is agreed that oral ansolysen, with or without serpasil, is a practicable treatment for these patients, it is then unreasonable to await developments of serious complications before instituting treatment.

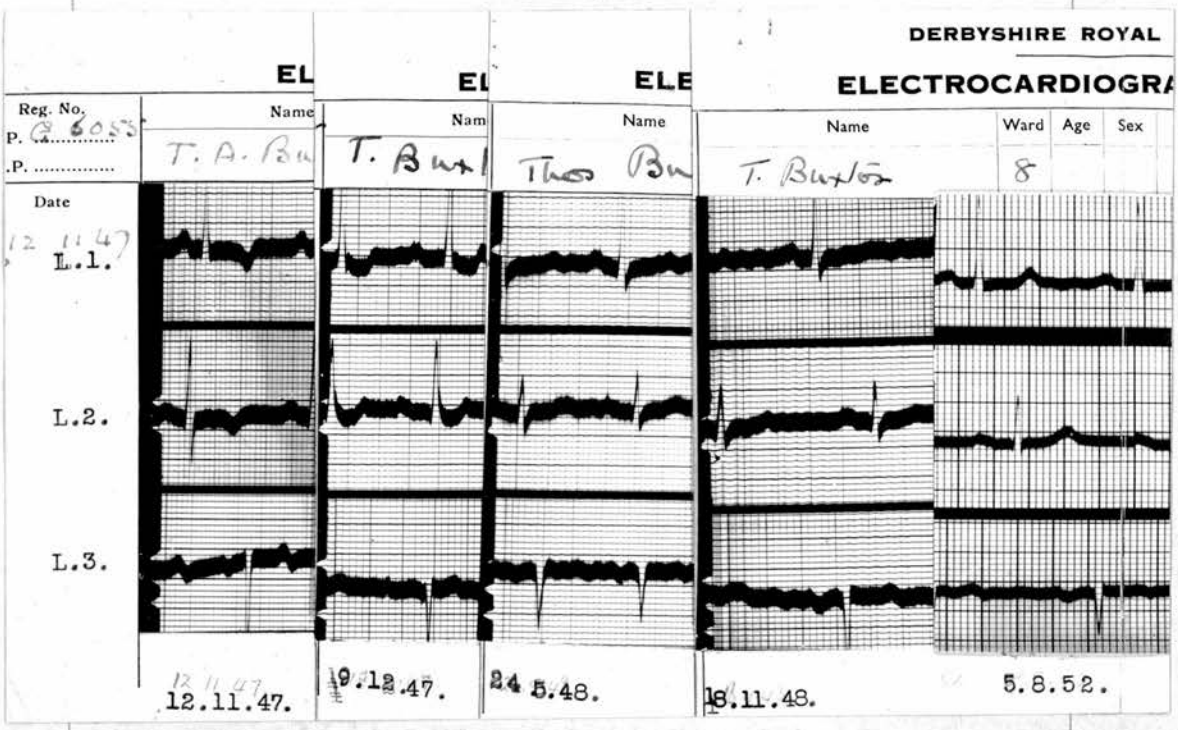
PLATE I.

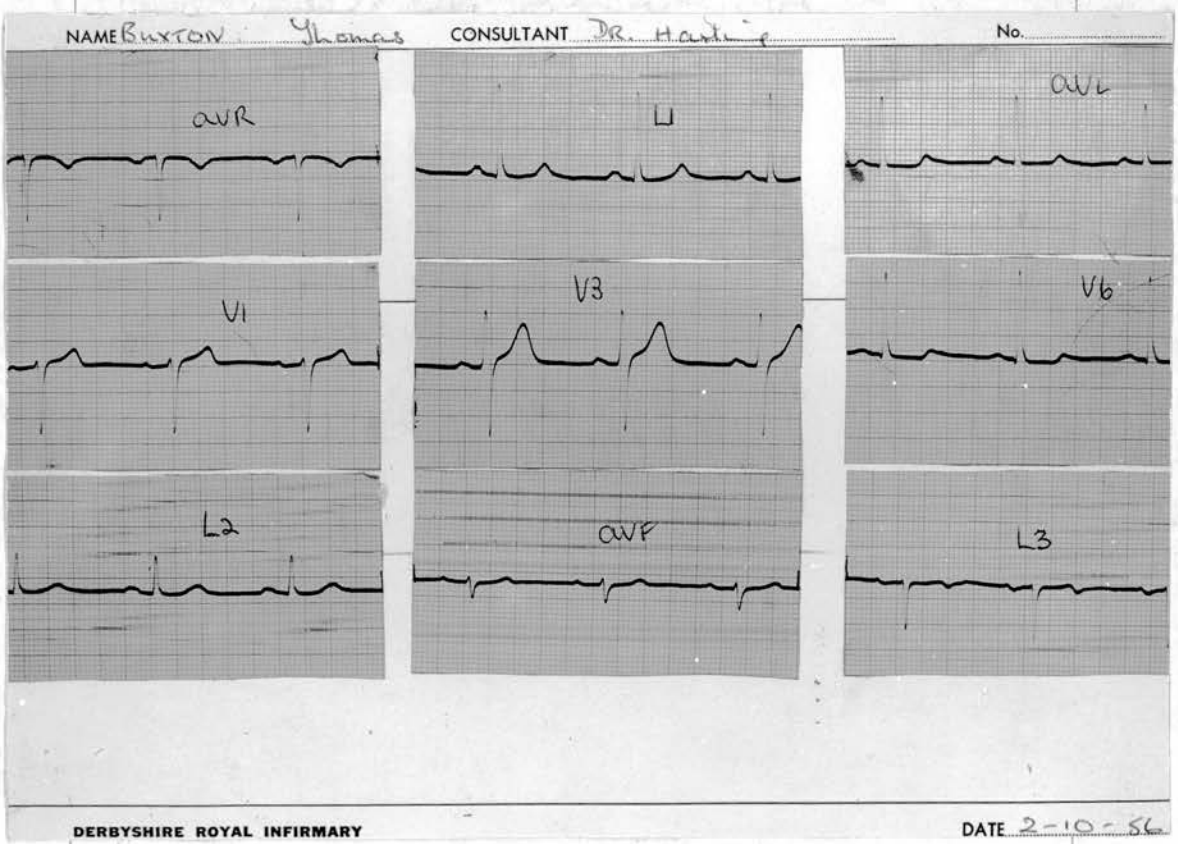


X-Ray Follow-up - Surgical Series.

F.55.R.L.D.S. 9.12.49.Initial B.P.200/140 marked enlargement of the heart seen in lower film. Good hypotension achieved after 2nd opn. (26.1.50) & heart size reduced 3 years later. Top film.

PLATE II.

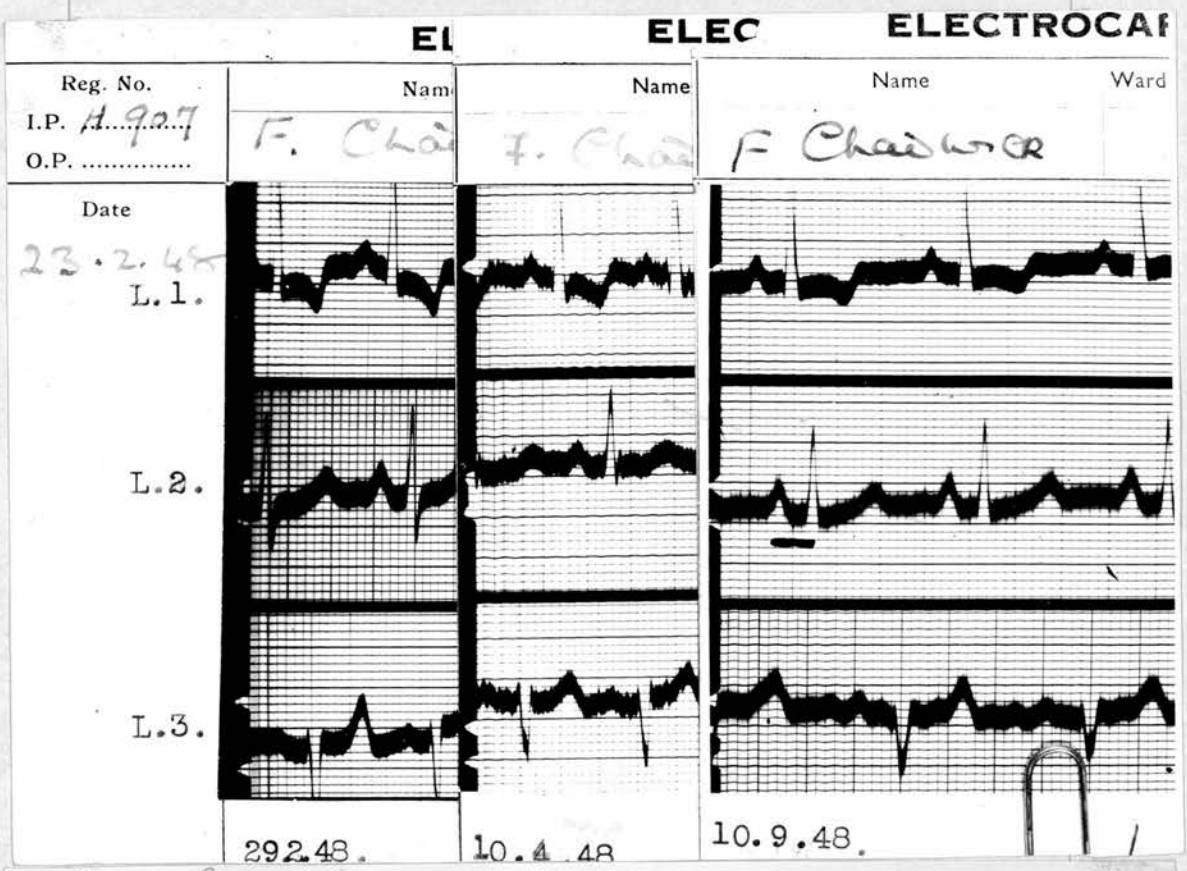


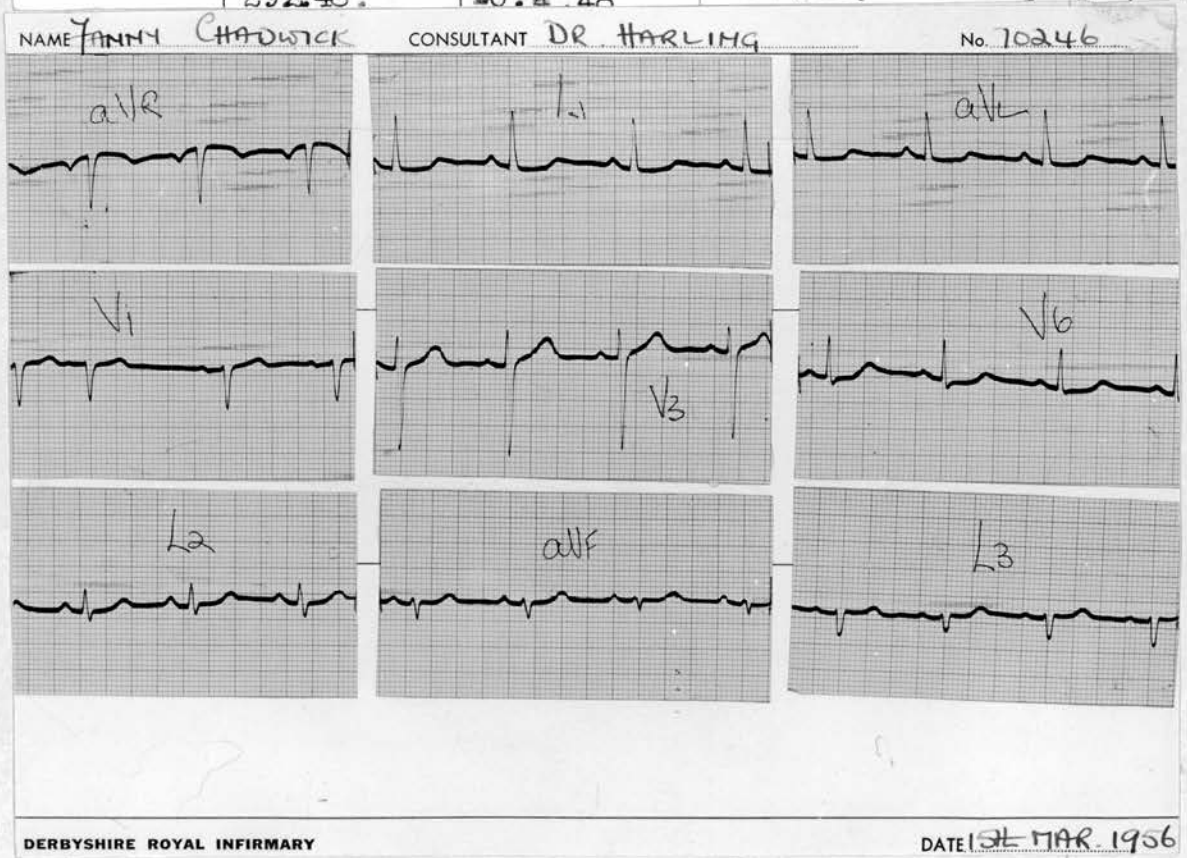


E.C.G. Follow-up. Surgical Series.

M.47. Group III. Initial Grade after Sokolow & Lyon marked - 3. Final grade 1. C.C.F. prior to 1st operation on 23.11.47. Operation failed to lower blood pressure but was symptomatically a great success.

PLATE III.

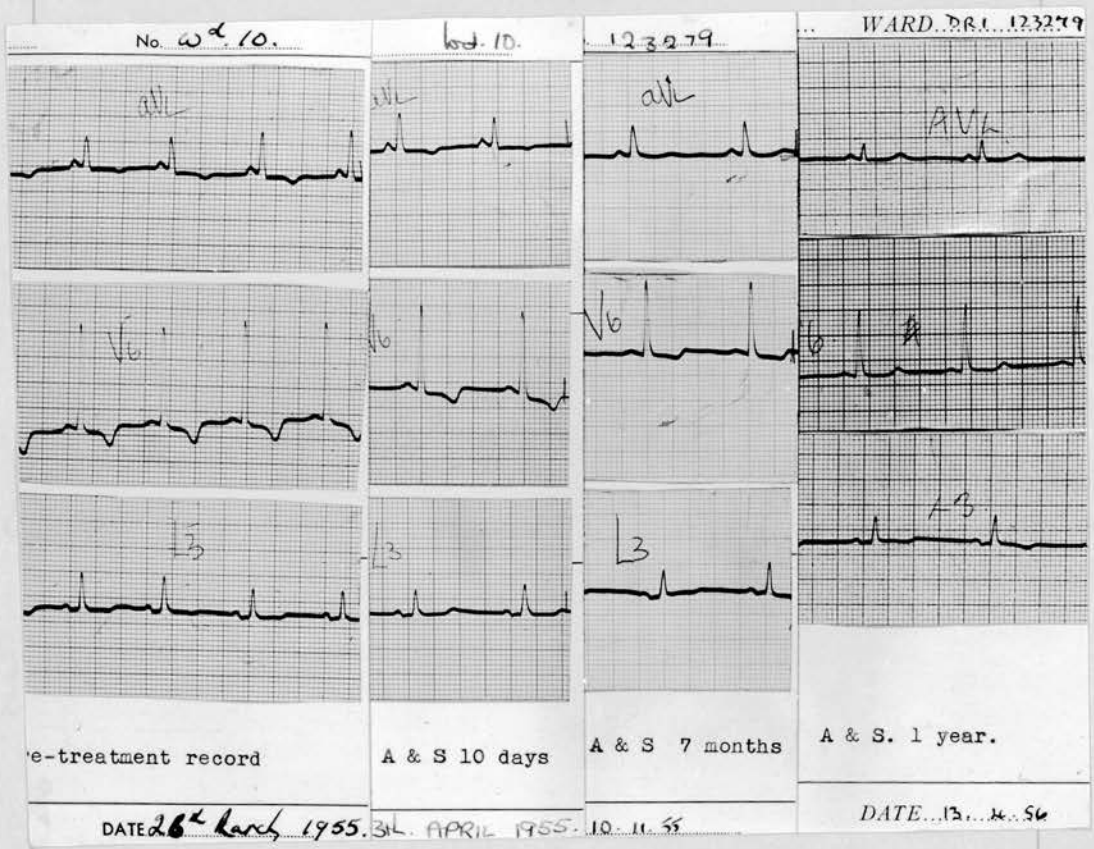




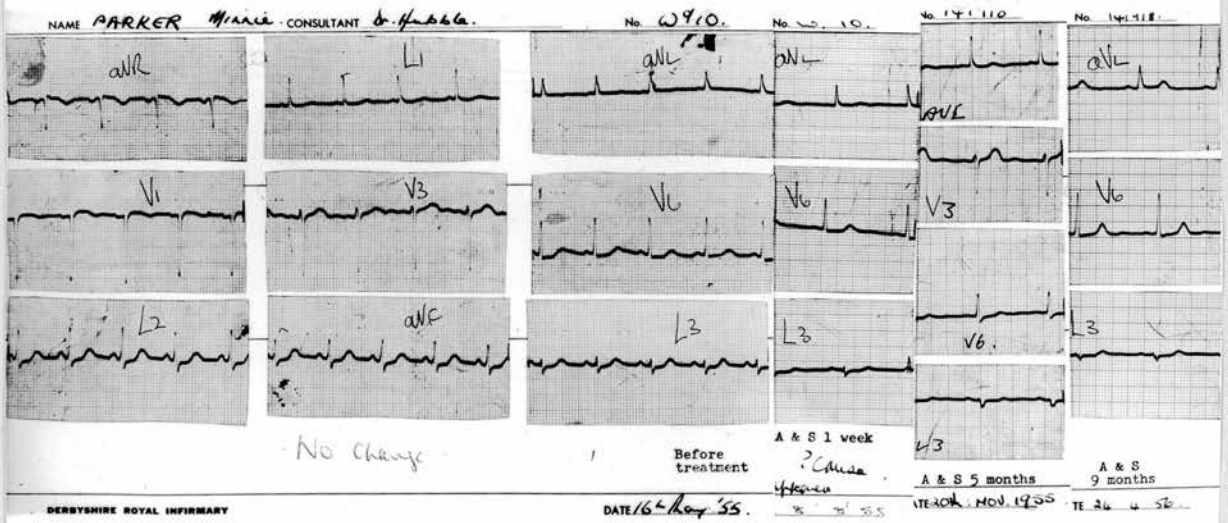
E.C.G. Follow-up. Surgical Series.

F.44. Group II. Initial Grade 3, final Grade 1.
R.L.D.S. 5.3.48. L.L.D.S. 30.3.48.
A temporary success in control of blood pressure.

PLATE IV.



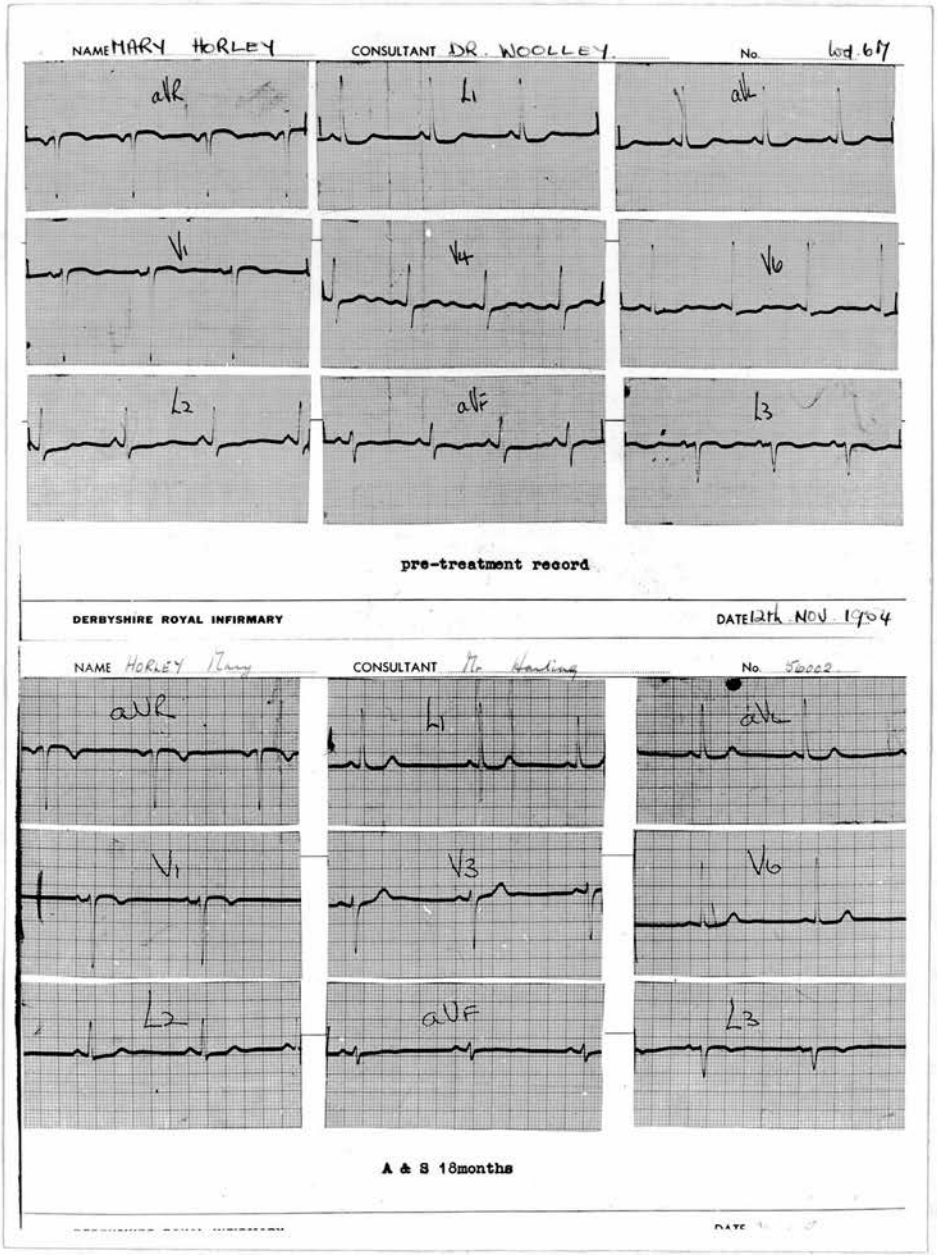
F.45. Group II. Initial Grade 3, final Grade 1.



E.C.G.Follow-up. Medical Series.

F.51. Group III. Initial Grade 1, final Grade 0.

PLATE V.



E.C.G. Follow-up. Medical Series.

F.39. B.P.220/170. Asymptomatic before treatment.
Initial Record Grade 1, final grade 1 minus.

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